CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-797

21-798

MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 03-28-05

FROM: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Division Director's Memorandum for NDA 21-797, entecavir 0.5 mg and 1.0 mg tablets, and NDA 21-798 entecavir oral solution for the Treatment of Chronic Hepatitis B Infection

1.0 Background

On September 30, 2004, Bristol-Myers Squibb Company (BMS) submitted New Drug Applications (NDAS) for entecavir (ETV) film-coated tablets and oral solution for treatment of chronic hepatitis B infection. Both applications received a priority review because it was determined that the drug product would be a significant improvement compared to marketed drugs for the same indication. The NDAs for entecavir were presented to an Antiviral Drugs Advisory Committee on March 11, 2005. Following discussion of the safety and efficacy data contained in the NDAs, the advisory committee voted unanimously to approve entecavir for treatment of chronic hepatitis B infection, based on its risk/benefit profile.

This memorandum summarizes the findings in the NDAs and is written in support of approval of these applications.

2.0 Summary of Efficacy

The efficacy of ETV was demonstrated in three phase 3 clinical trials in nucleoside naïve (022 and 027) and in lamivudine-refractory, e antigen positive subjects (026); trial 022 was also conducted in e antigen positive subjects and trial 027 was conducted in e antigen negative subjects. All studies were actively controlled with lamivudine. Doses of ETV were 0.5 mg once daily for the nucleoside naïve studies 022 and 027 and 1.0 mg once daily in lamivudine resistant subjects in 026. Dosage selection was rational and based on phase 2 studies.

The primary efficacy endpoint was similar to previous trials for other approved therapies for treatment of chronic hepatitis B infection. It was defined as a decrease from baseline of 2 points or more in the Knodell necroinflammatory score, with no concurrent worsening of the Knodell fibrosis score. Secondary endpoints were virologic, biochemical and serologic. They included: change from baseline in HBV DNA, proportion of patients with HBV DNA <400 copies/ml, proportion of patients with normalization of ALT, and proportion of patients with HBeAg loss, HBeAg seroconversion, HBsAg loss, and HBsAg seroconversion.

In the primary efficacy analysis in all three pivotal studies, ETV was shown to be statistically superior to lamivudine, the active control in the phase 3 studies. ETV was also superior to lamivudine for multiple secondary endpoints. These findings are summarized in the medical officer reviews by Drs. Linda Lewis and Yoshi Murata and in the statistical review by Dr. Tom Hammerstrom. Dr. Hammerstrom also conducted sensitivity analyses that underscored the robust treatment findings.

In addition to populations studied in the pivotal trials, BMS conducted Study 038, a placebo-controlled trial in HBV-HIV co-infected subjects that demonstrated ETV at a dose of 1.0 mg resulted in a 3.76 $\log_{10}$ copies/ml greater decrease from baseline log HBV DNA compared to placebo at week 24. Of note, only 3 patients randomized to receive ETV and no placebo patients achieved HBV DNA levels < 400 copies/ml at week 24. BMS also evaluated ETV in patients with decompensated liver disease in a trial that is ongoing. In a further attempt to examine a broader population, BMS conducted study 015, a small, open-label pilot study to evaluated ETV at a dose of 1.0 mg daily in subjects who had an orthotopic liver transplant who had recurrent HBV infection despite antiviral therapy. Although HBV DNA decreased by a mean of 3.62 $\log_{10}$ copies/ml, the study enrolled only nine subjects and is therefore too small to draw definitive conclusions.

3.0 Summary of Safety

The safety of ETV was demonstrated in 10 phase 2/3 studies comprising 1,497 subjects who received ETV and 899 subjects who received lamivudine. In general, ETV's adverse event profile, including laboratory abnormalities, was similar to lamivudine. Regarding safety, two areas were worth noting. The first was occurrence of malignancy in subjects treated with ETV compared to subjects receiving lamivudine. Malignancies were concerning because ETV was found to be a rodent carcinogen in two-year animal carcinogenicity studies. Tumors were seen at doses that were much higher multiples than doses proposed for approval. It is important to state that findings of a decreased rate of hepatocellular carcinoma in woodchucks infected with woodchuck hepatitis virus were critical to allowing further development of ETV. Please refer to the

pharmacology/toxicology review of Dr. Peter Verma for a detailed discussion of those studies.

A total of 37 subjects reported malignancies in the ETV development program. Similar rates occurred among ETV and lamivudine treated subjects. Specifically, 19/1497 (1.3%) occurred in subjects receiving ETV, and 9/899 (1%) occurred in lamivudine treated subjects; nine other patients reporting malignancies were in special study populations. Tumor types included: hepatocellular carcinoma, skin cancer, breast cancer, and prostate cancer. Tumors occurred over a period of time approximating 72 weeks. Some tumors recurred in patients who had a pre-existing condition. Of note, the application contained data on observational cohort studies commissioned by BMS to assess rates of malignancy in subjects not receiving ETV, but with a diagnosis of chronic hepatitis B infection. Rates in these observational studies were higher than that seen in the ETV development program to date. A pharmacovigilance study/program will be undertaken by the applicant to assess malignancy rates over time in subjects receiving ETV.

The second safety issue of hepatic flares is worthy of comment. A discussion of hepatic flares can be found in the medical officer's review and in the Team Leader memorandum by Dr. Katie Laessig. Briefly, on-treatment flares occurred at a rate of 2% and 4% in nucleoside naïve subjects receiving ETV and lamivudine, respectively. In lamivudine refractory subjects ALT flares occurred at a rate of 2% on the ETV arm and 11% in the lamivudine arm. Off-treatment flares of ALT tended to occur at higher rates than on-treatment flares. Specifically, off-treatment flares occurred at 6% and 10% in nucleoside naïve subjects receiving ETV and lamivudine, respectively. In lamivudine-refractory subjects, rates were 5% compared to zero in ETV and lamivudine-treated subjects, respectively. Of note, the sample size for the lamivudine refractory group was quite small.

A totals of 15 deaths occurred in the ETV development program. In the nucleoside naïve studies there were 6 deaths/1,347 subjects that occurred in two patients receiving ETV and 4 patients receiving lamivudine. In lamivudine-refractory studies there were also a total of 6 deaths: 4 in patients receiving ETV and 2 in those who received lamivudine. There were three additional deaths in supportive trials. None of the deaths were directly attributable to study drug except for a case of hepatic decompensation secondary to study drug withdrawal. The reviewing medical officers agreed with the applicant's assessment regarding causality of all of the deaths.

4.0 Summary of Virology

Please see the microbiology review of Dr. Lisa Naeger for complete details of the virologic findings of ETV, including a discussion of resistance. The following bullet points are taken from her review:

- Greater proportions of nucleoside-naïve subjects with chronic HBV infection achieved HBV DNA levels < 300 copies/mL on ETV treatment compared to LVD-refractory subjects.
- Genotypic or phenotypic evidence of resistance to ETV in nucleoside-naïve patients chronically infected with HBV has not been observed up to 48 weeks of 0.5 mg QD ETV treatment, including 2 subjects in 022 who experienced a confirmed virologic rebound.
- 7.4% (14/190) of LVD-refractory subjects treated with 1.0 mg ETV had evidence of emerging ETV-resistance substitutions by Week 48.
- ETV-resistance substitutions at rtI169, rtT184, rtS202, and/or rtM250 emerged concomitant with LVD–resistant mutations at rtL180 and/or rtM204 and can be associated with virologic rebound upon prolonged 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 emerging or present at BL
  - One isolate from study 015 who developed a rtT184A
  - One isolate from study 026 who developed a 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.
- A virologic response (viral load suppression below 300 copies/mL and > 2 $\log_{10}$ reductions in viral load) can occur in subjects with LVD-resistance in their HBV at baseline.
- Cross-resistance to ETV was not observed with adefovir-resistant HBV.
- HBV harboring ETV resistance-associated substitutions added to LVD resistance-associated substitutions did not regain susceptibility to LVD.

HBV resistance to ETV will continue to be monitored. The applicant will be asked to perform genotypic and phenotypic analyses of HBV DNA from patients receiving long-term entecavir therapy in ongoing clinical trials 022, 027, 026, 038, 048, and 901. Resistance data will also be requested on isolates from entecavir-treated patients with chronic HBV who experienced virologic rebound in serum HBV DNA levels in both the nucleoside-naïve and lamivudine-refractory studies.

5.0 Summary of Regulatory Issues

The following phase 4 commitments will be requested of the applicant:

1. Conduct and submit a final study report for a large simple safety study to assess the major clinical outcomes of death, progression of liver disease, and cancer in a broad population of HBV-infected patients using entecavir compared to standard of care over a period of 5 to 10 years of follow-up. The study should be randomized, stratified according to prior treatment, and of sufficient size to detect a 30% difference in cancer outcomes between the 2 groups. Monitoring by an independent Data Safety Monitoring Board is recommended.

2. Complete and submit the final study report for Study 048 comparing the efficacy and safety of entecavir to adefovir in patients with chronic HBV and decompensated liver disease.

3. Conduct and submit a final study report for a study of a larger efficacy and safety of entecavir in patients who are post-liver transplant. This study should enroll 50 to 100 patients and include analysis of virologic, biochemical, and serologic endpoints, evaluation of safety, and evaluation of HBV resistance.

4. Complete and submit the final study report for Study 038 evaluating the safety, efficacy, and resistance profile of entecavir in patients with HIV/HBV co-infection.

5. Complete and submit the final study reports for Studies 022, 027, and 026 and evaluate the safety and efficacy of entecavir compared to lamivudine during the second year of continued blinded study drug dosing.

6. Complete and submit the final study reports for Studies 901 and 049 to obtain long-term dosing (> 5 years for some subjects) and follow-up (> 5 years for some subjects) on entecavir use in patients rolled over from the Phase 2 and 3 clinical trials to address the following issues:

- maintenance of virologic suppression
- durability of HBeAg seroconversion and the rate of new events
- risk of drug-related adverse events including malignancy
- risk for development of resistance to entecavir

7. Continue to perform genotypic and phenotypic analyses of HBV DNA from patients receiving long-term entecavir therapy in ongoing clinical trials 022, 027, 026, 038, 048, and 901. Provide 96-, 144-, and 240-week data on the genotypic and phenotypic analyses of isolates from entecavir-treated patients with chronic HBV who experienced virologic rebound in serum HBV DNA levels in both the nucleoside-naïve and lamivudine-refractory studies.

8. Determine the in vitro susceptibility to ETV and ADV of substitutions at rtI169 alone and in the context of lamivudine- and ETV-associated resistance mutations and determine the in vitro susceptibility to ETV of tenofovir-associated resistance substitutions at rtA194 in a lamivudine-resistant background.

9. Conduct a study or substudy to determine entecavir exposure (PK profile) for pediatric patients from birth through 16 years of age to support dose-selection for the efficacy and safety assessment. Using selected doses, conduct an efficacy and safety study of entecavir in pediatric patients from birth through 16 years of age with efficacy based on the results of a variety of virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

10. Conduct and submit a final study report to evaluate the safety, efficacy, and resistance profile of entecavir used in combination with another oral anti-HBV therapy in treatment-naïve and treatment-experienced patients with chronic HBV to determine if there is any added benefit of combination therapy.

In addition, BMS will be asked to conduct and submit a final study report to evaluate the use of ETV in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (blacks/African Americans, Hispanics).

6.0 Recommendation

I concur with the findings of the multidisciplinary review team that the New Drug Applications for ETV film-coated tablets and solution should be approved. This determination was based on a review of the safety and efficacy data contained in these applications and the expert opinions of our advisory panel. ETV will provide another treatment in the armamentarium of therapies for chronic hepatitis B infection and will be indicated for a broad patient population including those with lamivudine-resistant disease and HBV-HIV co-infected subjects.

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/s/

Debra Birnkrant
3/28/05 02:41:08 PM
MEDICAL OFFICER

my dd memo. please sign off.

Edward Cox
3/29/05 08:49:59 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-797, 21-798
Submission Code	000
Letter Date	September 29, 2004
Stamp Date	September 29, 2004
PDUFA Goal Date	March 29, 2005
Reviewer Name	Linda L. Lewis, MD (Primary reviewer) Yoshihiko Murata, MD, PhD (Secondary reviewer)
Review Completion Date	March 29, 2005
Established Name	Entecavir
Trade Name	Baraclude™
Therapeutic Class	Nucleoside analogue
Applicant	Bristol-Myers Squibb
Priority Designation	P
Formulation	0.5 and 1 mg tablets 0.05 mg/mL oral solution
Dosing Regimen	0.5 or 1 mg once daily
Indication	Treatment of chronic hepatitis B virus infection
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is the opinion of the Medical Officers completing the Clinical Review of entecavir (ETV) that it should be approved for the treatment of chronic hepatitis B virus (HBV) infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum transaminases (ALT or AST) or histologically active disease. This recommendation is based on review of the efficacy and safety data submitted by Bristol-Myers Squibb (BMS or the applicant) in this NDA. No deficiencies were identified in the NDA submission that would preclude approval.

Entecavir was studied in 3 adequate and well-controlled clinical trials enrolling different key patient populations: nucleoside-treatment-naïve, hepatitis B e antigen positive patients, nucleoside-treatment-naïve, e antigen negative patients, and lamivudine (LVD)-resistant (or LVD-refractory), e antigen positive patients. Additionally, the applicant submitted results of 10 supporting clinical studies and 19 clinical pharmacology/pharmacokinetic studies. The FDA review confirmed that ETV was superior to LVD in achieving the primary endpoint of overall histologic improvement in liver biopsies over 48 weeks of dosing in each of these 3 study groups. Review of key virologic, serologic, biochemical, and composite secondary endpoints also supported the efficacy of ETV compared to LVD at 48 weeks. This treatment effect was consistent across subgroups analyzed according to gender, race, age, geographic region, and important HBV disease characteristics at baseline.

The FDA reviewers also concluded that ETV has been shown to be safe for its intended use as stated in the labeling by all tests appropriate to the safety review. The safety profile of ETV was similar to the active control LVD in each of the pivotal studies and in pooled nucleoside-naïve subjects and LVD-refractory subjects. Although the general safety and tolerability profile of ETV was comparable to that of LVD, concerns have been raised because ETV was shown to be carcinogenic in mice and rats who received the drug over their adult lifetimes at doses higher than those used in the clinical trials. In these animal carcinogenicity studies, male mice receiving ETV developed lung tumors at the equivalent of approximately 3 times the human dose. A variety of other tumors, including brain, vascular, and liver tumors were seen in mice and rats at dose equivalents 25-40 times the expected human dose. The clinical implication of these animal findings is currently unknown.

The assessment of risk-benefit for ETV must weigh the confirmed clinical efficacy and acceptable safety and tolerability profile against an unknown potential risk of cancer with longer-term use. This is a particularly complex assessment since HBV is an oncogenic virus and chronic HBV is known to be one of the most important risk factors for development of hepatocellular carcinoma. There is accumulating information from HBV treatment trials and from animal models of chronic HBV that treatment of the disease results in prevention or delay of development of the complications of chronic HBV including cirrhosis, need for liver

transplantation, and hepatocelllular carcinoma. Thus, the Review Team concurring with the unanimous decision of the Division of Antiviral Drug Products Advisory Committee concluded that the benefits of treatment with ETV outweighed the unknown risk of cancer suggested by the animal carcinogenicity findings. However, both the Review Team and the Advisory Committee believed that long-term use data will be needed to provide reassurance that ETV is not carcinogenic in humans.

The data submitted by the applicant were adequate to provide directions for use. The Phase 2 and Phase 3 development program provided sufficient data on which to base dose recommendations for a broad population of patients with chronic HBV. Studies evaluating the metabolism and excretion of ETV revealed that it is not extensively metabolized by the liver, is excreted almost entirely by the kidneys, and is unlikely to interact with other drugs. Clinical pharmacology studies conducted in patients with renal impairment provided sufficient information on which to base recommendations for dose adjustment in these patients based on their degree of renal impairment. A similar study in patients with hepatic impairment showed that dose adjustment in this patient population was not necessary.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The applicant has proposed a comprehensive pharmacovigilance program that will address the issues of cancer risk and serious hepatic adverse events following the approval of ETV. In addition to submitting the quarterly Periodic Adverse Drug Event Reports required for all new drugs, BMS has also agreed to submit Periodic Safety Update Reports (PSURs) every 6 months for the first 5 years of marketing. A summary and analysis of reported malignancies, serious hepatic events, and post-treatment exacerbations of hepatitis from ongoing clinical trials, observational studies, and spontaneous reporting will be included in the PSURs.

The pharmacovigilance plan also includes continued tracking of subjects completing the clinical trials through the ongoing rollover and observational studies, Studies 901 and 049. These studies will address the following issues: maintenance of virologic suppression, durability of HBeAg seroconversion and the rate of new events, risk of drug-related adverse events including malignancy, and risk for development of resistance to ETV.

The applicant has proposed conducting a large simple safety study to evaluate the occurrence of major events as ETV moves into broader clinical use. This post-marketing study is designed as a randomized, open-label, cohort study planned to enroll about 12,500 patients $\geq$ 16 years of age, randomized to receive either ETV or standard of care (any anti-HBV nucleoside or nucleotide chosen by their physician). Data will be gathered primarily from annual review of medical records and annual questionnaires. The outcomes to be analyzed will include all cause and cause-specific mortality, liver transplantation, and malignancy (all cancer, HCC, and non-liver cancer). The applicant proposes that the study will be monitored by an independent Data Safety

Monitoring Board and that interim analyses will be submitted to the FDA. The draft protocol for this study has been reviewed and discussed with consultants in the Division of Drug Risk Evaluation and we agree that the proposed study represents an appropriate effort on the applicant's part to collect important safety data. Strengths and limitations of the study have been discussed internally and with the applicant. The Review Team, DDRE, and the applicant will discuss details of the study design and statistical analyses when the final study protocol is submitted later this year.

Finally, BMS has proposed to track the outcomes of pregnant women who receive treatment with ETV through the mechanism of the established Antiretroviral Pregnancy Registry. This approach is considered appropriate by the Review Team and the registry's toll-free phone number will be included in the ETV label.

1.2.2 Required Phase 4 Commitments

The applicant has agreed to a series of Phase 4 (post-marketing) commitments designed to provide additional information regarding the durability of response to treatment with ETV, efficacy and safety in additional key patient populations including children, development of resistance in different patient populations, long-term risk of cancer, and the occurrence of significant hepatic complications. Some of the post-marketing commitments requested are for final study reports of studies that are already in progress, including the Phase 3 studies reviewed for this application. Under the Pediatric Research Equity Act we are deferring pediatric studies of ETV. Phase 4 commitments #8 and #9 listed below will fulfill the requirements of PREA. As pediatric development of ETV progresses, a reevaluation of the need for studies in children < 2 years of age will be conducted. The Phase 4 commitments are detailed below.

1. Conduct and submit a final study report for a large simple safety study to assess the major clinical outcomes of death, progression of liver disease, and cancer in a broad population of HBV-infected patients using entecavir compared to standard of care over a period of 5 to 10 years of follow-up. The study should be randomized, stratified according to prior treatment, and of sufficient size to detect a 30% difference in cancer outcomes between the 2 groups. Monitoring by an independent Data Safety Monitoring Board is recommended. Given the anticipated length of the study, it is recommended that the protocol will include plans to assess the adequacy of enrollment and submit interim reports of results at yearly intervals.
Protocol submission: July, 2005
Final report submission: July, 2016

2. Complete and submit the final study report for Study 048 comparing the efficacy and safety of entecavir to adefovir in patients with chronic HBV and decompensated liver disease.
Protocol submission: study ongoing
Final report submission: October, 2008

3. Conduct and submit a final study report for a larger efficacy and safety study of entecavir in patients who are post-liver transplant. This study should enroll 50 to 100 patients and include

analysis of virologic, biochemical, and serologic endpoints, evaluation of safety, and evaluation of HBV resistance.
Protocol submission: December, 2005
Final report submission: December, 2008

4. Complete and submit the final study report for Study 038 evaluating the safety, efficacy, and resistance profile of entecavir in patients with HIV/HBV co-infection.
Protocol submission: study ongoing
Final report submission: July, 2006

5. Complete and submit the final study reports for Studies 022, 027, and 026 and evaluate the safety and efficacy of entecavir compared to lamivudine during the second year of continued blinded study drug dosing.
Protocol submission: studies ongoing
Final report submissions: October, 2006

6. Complete and submit the final study reports for Studies 901 and 049 to obtain long-term dosing ($\geq$ 5 years for some subjects) and follow-up ($\geq$ 5 years for some subjects) on entecavir use in patients rolled over from the Phase 2 and 3 clinical trials to address the following issues:

- maintenance of virologic suppression
- durability of HBeAg seroconversion and the rate of new events
- risk of drug-related adverse events including malignancy
- risk for development of resistance to entecavir

Protocol submission: studies ongoing
Final report submission: July, 2011

7. Continue to perform genotypic and phenotypic analyses of HBV DNA from patients receiving long-term entecavir therapy in ongoing clinical trials 022, 027, 026, 038, 048, and 901. Provide 96-, 144-, and 240-week data on the genotypic and phenotypic analyses of isolates from entecavir-treated patients with chronic HBV who experienced virologic rebound in serum HBV DNA levels in both the nucleoside-naïve and lamivudine-refractory studies.
Protocol submissions: studies ongoing
Report submissions: Summary reports of overall consecutive resistance analyses submitted annually.

8. Conduct a study or substudy to determine entecavir exposure (PK profile) for pediatric patients from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.
Protocol submission: December, 2005
Final report submissions: July, 2007

9. Using doses selected based on study/substudy described in #8, conduct an efficacy and safety study of entecavir in pediatric patients from birth through 16 years of age with efficacy based on the results of a variety of virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

Protocol submission: July, 2007
Final report submissions: December, 2009

10. Conduct and submit a final study report to evaluate the safety, efficacy, and resistance profile of entecavir used in combination with another oral anti-HBV therapy in treatment-naïve and treatment-experienced patients with chronic HBV to determine if there is any added benefit of combination therapy.
Protocol submission: December, 2005
Final report submission: December, 2009

11. Determine the *in vitro* susceptibility to ETV and ADV of substitutions at rtI169 alone and in the context of lamivudine- and ETV-associated resistance mutations and determine the *in vitro* susceptibility to ETV of tenofovir-associated resistance substitutions at rtA194 in a lamivudine-resistant background.
Final report submission: July, 2006

12. Conduct and submit a final study report to evaluate the use of ETV in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (blacks/African Americans, Hispanics).
Protocol submission: December, 2005
Final report submission: December, 2008

1.2.3 Other Phase 4 Requests

Aside from the Phase 4 commitments listed above, no other recommended or optional Phase 4 commitments have been requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Entecavir (trade name Baraclude™) is a guanosine nucleoside analogue that has been developed for the treatment of adults with chronic HBV infection and evidence of active liver inflammation. It will be available as 0.5 mg and 1 mg tablets and as an oral solution containing 0.05 mg/mL (0.25 mg/5 mL). All Phase 3 clinical trials were conducted using the 0.5 mg tablet. At this time, the oral solution is intended for use in adult patients who cannot swallow tablets or who require dose adjustment because of renal impairment.

The primary efficacy and safety review of ETV is based on the results of 3 Phase 3 clinical trials and additional subjects from the to-be-marketed dose levels of one Phase 2 study. In all of these studies ETV was compared to LVD at the approved dose of 100 mg once daily. The 3 Phase 3 studies used a similar primary efficacy endpoint: the proportion of patients in each treatment

group who achieved a ≥ 2 point decrease in the Knodell necroinflammatory score with no worsening of the Knodell fibrosis score on liver biopsy at Week 48 compared to baseline. All 4 of the pivotal studies evaluated a series of virologic, serologic, biochemical, and composite endpoints at Week 48. These studies are described briefly below:

- Study AI463022 was a multinational, randomized, active-control study (using ETV and LVD placebos) comparing ETV 0.5 mg once daily to LVD in nucleoside-treatment-naïve, hepatitis B e antigen positive adults with compensated liver disease. A total of 715 patients were enrolled in this study and 709 actually received blinded study drug and were included in all safety and efficacy analyses. Primary analyses were conducted after the first 48 weeks of dosing.

- Study AI463027 was a multinational, randomized, active-control study (using ETV and LVD placebos) comparing ETV 0.5 mg once daily to LVD in nucleoside-naïve, hepatitis B e antigen negative adults with compensated liver disease. A total of 648 patients were enrolled in this study and 638 actually received blinded study drug and were included in all safety and efficacy analyses. Primary analyses were conducted after the first 48 weeks of dosing.

- Study AI463026 was a multinational, randomized, active-control study (using ETV and LVD placebos) comparing ETV 1 mg once daily versus continued LVD treatment in hepatitis e antigen positive adult patients with compensated liver disease who had persistent HBV viremia in spite of treatment with LVD (termed LVD-refractory). A total of 293 patients were enrolled in this study and 286 actually received blinded study drug and were included in all safety and efficacy analyses. Primary analyses were conducted after the first 48 weeks of dosing.

- Study AI463014 was a multinational, randomized, active control study comparing 3 doses of ETV (0.1 mg, 0.5 mg, and 1 mg) once daily to LVD in adult LVD-refractory patients with compensated liver disease. In order to increase the size of the safety database for LVD-refractory patients, the cohorts receiving ETV 1 mg and LVD were included in the primary review. A total of 47 patients received ETV 1 mg and 45 received LVD and were included in the LVD-refractory cohort assessments. Primary analyses in this study were conducted at 24 weeks with an extension beyond 48 weeks for those who showed a virologic response to blinded treatment.

In the Phase 3 studies approximately 93% (Study 022), 95% (Study 027) and 90% (Study 026) of enrolled patients completed 48 weeks of blinded study dosing and had their Week 48 clinical assessment.

In addition, 2 smaller studies evaluated the use of ETV in treatment of chronic HBV in other key patient populations. These studies did not rely on liver biopsy for assessment of efficacy but did perform a similar series of virologic, serologic, biochemical, and composite endpoint analyses at 48 weeks. These studies include:

- Study AI463038 a randomized, placebo-controlled study comparing ETV to placebo in HIV/HBV co-infected patients with compensated liver disease receiving LVD as part of the antiretroviral therapy. A total of 68 patients were randomized, 51 received ETV 1 mg once daily and 17 received placebo over 24 weeks of blinded treatment. After 24 weeks, all patients were allowed to continue open-label ETV.

- Study AI463015 was a small, open-label, pilot study enrolling 9 liver transplant recipients who had compensated liver disease and recurrent HBV viremia in spite of post-transplant HBV prophylaxis. The primary objective of this study was to assess the pharmacokinetics and safety of ETV in this population.

1.3.2 Efficacy

The primary efficacy endpoint for the Phase 3 studies was histologic improvement in the Week 48 liver biopsy compared to the baseline biopsy, defined as $\geq$ 2 point improvement in Knodell necroinflammatory score with no worsening in the Knodell fibrosis score. The FDA statistical analysis confirmed the applicant's analysis of the primary efficacy endpoint. Although the studies were originally designed to show equivalence of ETV to LVD, the analysis demonstrated that a significantly greater proportion of subjects receiving ETV experienced overall histologic improvement compared to LVD in all of the Phase 3 studies. In addition, ETV was superior for each of the individual components of the overall histologic improvement.

Review of key secondary endpoints also supported the efficacy of ETV compared to LVD. ETV was shown to be superior to LVD in all analyses evaluating changes in HBV DNA over 48 weeks using 2 different assays to measure HBV DNA. FDA review confirmed the applicant's conclusions that a greater proportion of ETV subjects than LVD subjects achieved HBV DNA < 400 copies/mL and ETV subjects achieved greater mean decreases in HBV DNA using the PCR assay. Virologic responses were superior for ETV-treated subjects compared to LVD-treated subjects in all of the Phase 3 studies. Other key secondary endpoint analyses concluded that ETV was superior or equivalent to LVD through 48 weeks for the proportion of subjects achieving normalization of ALT (ALT < 1 x the upper limit of normal) and the proportion with improvement in Ishak fibrosis score (another histologic method of assessing liver fibrosis).

The supportive study conducted in HIV/HBV co-infected subjects demonstrated that in patients with LVD-refractory HBV receiving LVD as part of their HIV therapy, ETV had a significant effect on HBV DNA levels through 24 weeks of dosing. A small proportion of these co-infected subjects achieved HBV DNA < 400 copies/mL by Week 24 and a relatively small proportion achieved normalization of ALT. Similarly, the small, pilot study conducted in liver transplant recipients suggested that this cohort of patients could achieve significant decreases in HBV DNA when treated with ETV.

An assessment of efficacy for an antiviral drug is incomplete without an evaluation of the risk of emergence of resistance. In the case of ETV, the applicant has conducted a variety of laboratory and clinical resistance studies. The major conclusions have been confirmed by FDA virologists and include several key points. In laboratory testing, ETV is cross-resistant with LVD but not

adefovir (ADV). This cross-resistance with LVD is the reason why LVD-refractory patients require a higher dose of ETV than those who are nucleoside-naïve. No ETV resistance has been detected in ETV-treated, nucleoside-naïve patients at 48 weeks but longer term data are needed to determine what mutations will emerge on ETV treatment and to determine the pathway to ETV resistance in naïve subjects. Mutations at amino acids I169, T184, S202 and M250 of the HBV polymerase are associated with ETV resistance both individually and in combination but, to date, these ETV-associated resistance mutations have emerged only when LVD-resistant mutations at L180 and/or M204 were present at baseline. These ETV resistant mutations were associated with virologic rebound in a majority of patients. Follow-up in these patients is ongoing.

Although the database supporting the efficacy of ETV was extensive and included several key patient populations, there were some limitations of the data. As noted in the clinical review, the small number of blacks/African Americans enrolled in the clinical development program did not provide sufficient evidence to determine whether they respond differently to treatment with ETV. Also, ETV has not yet been evaluated in pediatric patients with chronic HBV. Although the data from the pilot study in liver transplant recipients was encouraging, the size of that study makes it difficult to draw conclusions about the efficacy of ETV in this population. There were no data submitted in the NDA regarding the efficacy of ETV in patients with decompensated liver disease due to chronic HBV infection, another important subgroup. Finally, although the results of these studies support the superiority of ETV treatment compared to LVD treatment by a variety of histologic, serologic, virologic, and composite endpoints measured at 48 weeks, there were no data comparing ETV to ADV, the other approved drug for the treatment of chronic HBV. These areas of interest need to be investigated and will be addressed either in post-marketing commitments or by ongoing studies. None of these limitations in the database preclude approval of ETV.

1.3.3 Safety

FDA reviewers evaluating the clinical safety data concluded that the safety profile of ETV was similar to that of LVD in each of the 4 pivotal studies and in pooled nucleoside-naïve subjects and LVD-refractory subjects. Adverse events (AEs) were reported frequently in the nucleoside-naive patients (about 81% in both arms) but there were few differences in the pattern of AEs reported by ETV-treated patients compared to LVD-treated patients. The pattern of AEs was very similar in the LVD-refractory patients, with over 80% subjects reporting some AE. The most commonly reported events in ETV-treated subjects included: headache, upper respiratory infection, nasopharyngitis ("common cold"), fatigue, cough, abdominal pain, and arthralgia. Many of these events are common in the general population and in the population of patients with chronic HBV. Most of the reported AEs in both treatment groups were mild in intensity and considered unrelated to study drug. Relatively few AEs of moderate to severe intensity were considered drug-related in either treatment group. Among those most commonly considered drug-related were: headache, fatigue, nausea, abdominal pain, and clinically significant abnormalities of ALT, AST, amylase, and lipase. Many of these events were numerically more frequent in LVD-treated subjects than ETV-treated subjects.

Three categories of adverse events deserve increased attention because of either the potential seriousness of the events or signals from animal toxicology studies: acute exacerbations of hepatitis (ALT flares), nervous system or neurologic AEs, and malignancies. To date, none of these events has been shown to occur more frequently among ETV-treated subjects compared to LVD-treated subjects.

Exacerbations of hepatitis or flares are a well-known complication of chronic HBV and its treatment and have been documented during and after treatment with all of the approved drugs. ALT flares were documented infrequently in nucleoside-naïve patients during the on-treatment period but occurred more often in subjects receiving LVD (2% ETV, 4% LVD). In nucleoside-naïve patients, ALT flares were again documented more often among LVD subjects (4% ETV, 8% LVD) during off-treatment follow-up. ALT flares were documented more often among patients in the LVD-refractory trials. In this population, 2% of ETV subjects and 10% of LVD subjects experienced ALT flares while receiving study drug. The number of LVD-refractory subjects followed off-treatment was too small to make definitive conclusions regarding rates of ALT flares in this setting.

Nervous system toxicity was identified in one of the pre-clinical animal toxicology studies of ETV and there appeared to be a dose-response relationship for these events identified in the Phase 2 studies. However, in the pivotal studies, rates of all neurologic events were similar across treatment groups in both nucleoside-naïve and LVD-refractory subjects. There were no significant differences in the proportions of subjects reporting anxiety, dizziness, headache, insomnia, migraine, paresthesia, somnolence or syncope across treatment groups. No significant pattern of ETV-related neurologic AEs could be identified.

The occurrence of malignancies during ETV use was of special interest during the review process because of the rodent carcinogenicity study findings and because chronic HBV is known to be a strong risk factor for development of hepatocellular carcinoma. A review of all cases of malignancy reported during the ETV development program identified 37 subjects with malignancies. Of these subjects, 28 were in the randomized clinical trials populations occurring in 1.3% of ETV-treated subjects and 1% of LVD-treated subjects. The most commonly reported malignancy was hepatocellular carcinoma, occurring in 9 (0.6%) ETV subjects and 4 (0.4%) LVD subjects. Other malignancies occurring in more than one subject included: gastric carcinoma, basal cell carcinoma, prostate cancer, and breast cancer. Continued evaluation of malignancies during ETV use is likely to require study over many years and will be addressed in post-marketing commitments.

A total of 15 deaths occurred during treatment with study drugs during all of the ETV studies submitted in the NDA. Across the pivotal trials, 12 deaths were balanced between patients receiving ETV and those receiving LVD. None of the deaths were considered by the local physicians to be related to study drugs but one death was thought to be possibly related to withdrawal of study drug and resulting hepatic decompensation. The number of patients who developed other serious AEs (eg., death, hospitalization, cancer, congenital anomaly, life-threatening condition, or other medically significant event) while on study was relatively small. In the pivotal studies, the rate of on-treatment SAEs in nucleoside-naïve subjects (7% ETV, 8%

LVD) and LVD-refractory subjects (10% ETV, 7% LVD) was comparable across the treatment arms.

Because of their mechanism of action, nucleoside analogue drugs such as ETV have low potential for abuse or for withdrawal phenomena and ETV is unlikely to interact with other drugs that have abuse or withdrawal potential. To date, there are no data regarding overdose with ETV. Doses up to 20 mg/day have been evaluated in small, 2 week pharmacokinetic studies and found to be generally safe.

1.3.4 Dosing Regimen and Administration

Review of the data provided in the NDA supports the approval of ETV for treatment of chronic HBV at doses of ETV 0.5 mg once daily in nucleoside-naïve adult patients and ETV 1 mg once daily in LVD-refractory adult patients. The results of the pivotal studies support these doses and the once daily dosing interval is well-supported by the pharmacokinetic data.

There were no differences in drug exposure based on gender. Minor increases in ETV exposure in elderly subjects compared to younger subjects is most likely attributed to changes in renal function in that population and no specific age-related dose adjustments are necessary. Differences in ETV exposure in Asians and non-Asians are most likely related to differences in body weight and no dose adjustment based on race is necessary.

Additionally, food effect studies suggest that ETV should be taken on an empty stomach for best absorption. It is recommended that ETV be taken at least 2 hours after a meal and at least 2 hours before the next meal.

1.3.5 Drug-Drug Interactions

No specific ETV drug-drug interactions are anticipated based on its metabolism. Since it is not extensively metabolized in the liver, it is unlikely to interact with drugs utilizing the cytochrome P450 system. It is not a substrate for p-glycoprotein and is also unlikely to compete with drugs utilizing this transporter system. There are no significant interactions between ETV and the other approved drugs for chronic HBV (LVD and ADV) in clinical pharmacology studies or the other nucleoside analogues used to treat HIV in laboratory studies.

1.3.6 Special Populations

The applicant evaluated ETV exposure in subjects with renal impairment including those requiring hemodialysis and continuous ambulatory peritoneal dialysis (CAPD). In these subjects, as renal function declined, ETV half-life lengthened and ETV drug concentrations increased compared to subjects with normal renal function. Hemodialysis removed about 13% of the ETV dose and CAPD removed < 1% over 7 days in subjects with severe renal impairment. Based on these findings, dosage reduction of ETV is needed in the presence of renal impairment.

Based on reanalysis of the modeling and simulation data, the FDA Clinical Pharmacology reviewer concluded that the applicant's original proposal for dosing patients requiring hemodialysis or CAPD would result in ETV drug levels much higher than the levels in patients with normal renal function. We suggested decreasing the recommended ETV dose in this group but agreed with the applicant's proposed dose adjustments for other degrees of renal impairment. The dose recommendations for patients with renal impairment will require use of the ETV oral solution (0.05 mg/mL) but should be simple to accomplish with this formulation.

ETV has been studied in a small number of liver transplant recipients with recurrent HBV post-transplant (Study 015). This study was too small to reach conclusions regarding the efficacy and safety of ETV in this population. No specific safety concerns were raised by the data available from this cohort of subjects and decreases in HBV DNA were documented. However, mean ETV concentration in this cohort was approximately twice that of healthy subjects receiving the dose of 1 mg ETV. This increase in drug exposure in liver transplant recipients was consistent with their degree of renal impairment. Based on this limited information, no dose adjustment (other than that for renal function) is suggested in liver transplant recipients should they need to receive ETV.

Recommendations for dosing in HIV/HBV co-infected patients who have previously received LVD are based on the results of Study 038. As for other LVD-refractory groups, a dose of ETV 1 mg is proposed for HIV/HBV co-infected patients who have received prior LVD treatment. No pharmacokinetic evaluations were conducted during this study but the selected dose clearly had a beneficial effect on HBV DNA levels after 24 weeks of dosing compared to placebo. No specific safety concerns were raised in this cohort of subjects. This study is still ongoing and additional data will be available through another 24 weeks of open-label dosing.

The clinical trials did not assess ETV use in women who were pregnant or breastfeeding. The animal reproductive toxicology studies suggest that there is a large margin of safety in administering ETV to pregnant animals. In the post-marketing stage, it is very likely that ETV will be taken by women who may be or may become pregnant while receiving the drug. The applicant has made arrangements to participate in a national registry for pregnant women who receive treatment for HIV (the Antiretroviral Pregnancy Registry). This seems appropriate since many of the antiretroviral drugs are nucleoside analogues and both of the other drugs approved for treatment of HBV are included in the registry.

To date, the use of ETV for the treatment of chronic HBV in pediatric patients has not been evaluated. After the results of the rodent carcinogenicity studies were reported, the Review Team asked BMS to delay its pediatric development program until 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. Now that the NDA review confirms that ETV is superior to LVD by many efficacy measures and the general safety and tolerability profile is comparable, we believe the applicant should proceed with a pediatric development plan. Since an oral solution formulation will be available, the pediatric development program is essential to allow safe use of the drug in this population and limit the potential dangers of off-label use.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Entecavir is a guanosine nucleoside analogue that has been developed for the treatment of adults with chronic hepatitis B virus (HBV) infection.

Generic (trade) name: Entecavir (Baraclude), abbreviated as ETV throughout this review

Chemical class: New molecular entity

Pharmacological class: Nucleoside analogue, inhibitor of HBV polymerase

Proposed indication, dosing regimens, and age groups: the proposed indication is for the treatment of chronic HBV in adults with evidence of — recommended dose for nucleoside treatment-naïve patients is 0.5 mg once daily, recommended dose for patients with persistent HBV viremia while receiving lamivudine (LVD) or with evidence of LVD-resistant HBV is 1 mg once daily, indication for adults and adolescents > 16 years of age

2.2 Currently Available Treatment for Indications

At present, there are 3 approved treatments for chronic HBV infection marketed in the U.S.: interferon-alpha (IFN), LVD, and adefovir dipivoxil (ADV). IFN is a naturally-occurring cytokine that acts as an immune modulator. It was approved for the treatment of chronic HBV in 1992. It requires parenteral administration and has a side effect profile that includes flu-like symptoms, fever, malaise, myalgias, and autoimmune disorders. LVD, the first oral, nucleoside analogue approved for the treatment of HBV, represents a cytosine analogue and was approved in 1998. It is well-tolerated but long-term use has been hampered by the predictable emergence of resistance in the HBV of patients taking the drug at rates of about 20% per year. ADV, an acyclic nucleotide phosphonate analogue, was approved for the treatment of HBV in 2002. For the purposes of this review, ADV is considered to be in the same class as nucleosides. ADV has been associated with dose-related renal toxicity and this adverse drug effect has limited use of the drug in subgroups of patients with chronic HBV and renal impairment and those requiring other nephrotoxic drugs.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity that is not currently marketed in the U.S.

2.4 Important Issues With Pharmacologically Related Products

As noted above, 2 other nucleoside analogues have been approved for the treatment of chronic HBV infection. Nucleoside analogues used as HIV reverse transcriptase inhibitors (NRTIs) have

also been developed as the backbone of multi-drug regimens for the treatment of HIV infection and as such, there is significant experience with the use of the drugs in chronically ill patients, either alone or in combination with other medications.

As a class, the NRTIs have been noted to have adverse effects stemming from interference with human mitochondrial DNA. These effects include: pancreatitis, lactic acidosis, peripheral neuritis, and the fat redistribution syndromes seen with highly active antiretroviral therapy. LVD and ADV have not been noted to be as prone to these effects as some of the other nucleosides.

Among NRTIs, there is evidence of cross-resistance in HIV developing with extended use. Both LVD and ADV have activity against HIV and LVD was approved initially as an antiretroviral drug before its development as anti-HBV treatment. LVD is cross-resistant with some of the other NRTIs. ADV and LVD do not appear to be cross-resistant for HBV by in vitro assays.

2.5 Presubmission Regulatory Activity

The initial protocol for development of ETV for the treatment of chronic HBV was submitted as IND 52,196 in December, 1996. Development of the drug proceeded through pre-clinical testing, Phase 1 and Phase 2 studies with the Review Division providing feedback on protocol design, endpoints, safety monitoring, and appropriate study populations via fax and telephone communications. An End-of-Phase-2 meeting was held with the applicant in December, 2000, during which BMS presented summary data of their 4-week and 24-week dose-finding studies in nucleoside-naïve subjects (Studies 004 and 005) and in those with persistent HBV viremia while receiving LVD (termed LVD- refractory, Study 014). Dose selection for the Phase 3 studies was discussed with agreement that the applicant should proceed with their planned doses of ETV 0.5 mg once daily in nucleoside-naïve subjects and 1 mg once daily in LVD-refractory subjects. A CMC End-of-Phase-2 meeting was held in December, 2002, at which many of the pre-submission CMC issues were addressed and agreed upon.

The Review Division began communicating with the applicant regarding the results of rodent carcinogenicity studies in 2001 when preliminary interim analysis of the mouse carcinogenicity study revealed that there was an increased rate of pulmonary tumors. Because these findings were preliminary and because the in vitro activity of ETV, the results of woodchuck hepatitis model studies, and the Phase 2 study results were extremely promising, it was decided to incorporate the animal findings in the Informed Consent forms for the clinical trials and continue with the Phase 3 studies. The final study reports of the 2-year mouse and rat carcinogenicity studies were submitted to the IND in July, 2002, and reviewed by Dr. Pritam Verma, the Pharmacology/Toxicology Reviewer (see Section 3.2 Animal Pharmacology/Toxicology for a summary of the study results). He considered ETV to represent a potential cancer risk to humans based on the results of the rodent studies. The results of the studies were presented to the Executive Carcinogenicity Assessment Committee in June, 2003, who agreed with Dr. Verma's conclusion. These conclusions were relayed to BMS with the additional information that the Review Team believed that the animal data would need to be evaluated in the context of the other pre-clinical data and the promising clinical data as part of a thorough risk-benefit

assessment of ETV. In a conference call in September, 2003, the Review Team recommended that BMS delay initiation of its pediatric development program until a full assessment of the risk-benefit of ETV in adults could be completed.

The applicant met with the Review Division on three occasions to discuss the submission of the ETV NDA and the data submitted. In early 2004, the applicant and the Review Team reached agreement on the format of the NDA electronic datasets and a preview of the datasets was provided. These electronic datasets appeared to meet the needs of the primary reviewers from all disciplines. A clinical pre-NDA meeting was held in April, 2004, to discuss the contents and format of the NDA submission. In a separate meeting with the Review Team in September, 2004, the applicant reviewed their rodent carcinogenicity study findings as well as the results of several additional studies to determine the mechanism of potential carcinogenicity. At that meeting it was suggested that if the applicant did not agree with the Review Division's assessment of ETV's carcinogenic potential in humans, they had the option to present the carcinogenicity findings to the Full Carcinogenicity Assessment Committee. This suggestion was accepted and BMS met with the Full CAC in January, 2005. After reviewing the animal study results and hearing the applicant's additional data the Full CAC decided that the rodent tumors identified in the carcinogenicity studies were relevant to the human safety evaluation.

2.6 Other Relevant Background Information

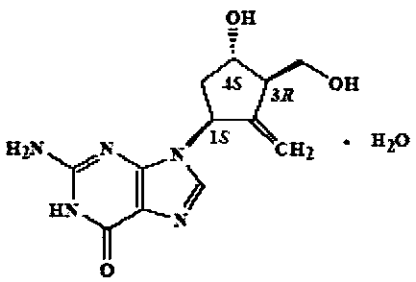
At this time, no additional information is available from regulatory actions in other countries. To our knowledge, ETV has been submitted for regulatory review in the European Union and in China. Submissions to other national regulatory authorities are planned.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Chemical name (IUPAC): 2-amino-1,9-dihydro-9-[(*1S,3R,4S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-6*H*-purin-6-one, monohydrate

Chemical structure:



Chemical formula: $C_{12}H_{15}N_5O_3 \cdot H_2O$

Molecular weight: 295.3

Formulations: 0.5 mg and 1 mg tablets
Oral solution containing 0.05 mg/mL

For full details regarding review of the chemistry, manufacturing, and controls data submitted in the NDA, please see the Chemistry Review conducted by Dr. Lorenzo Rocca. As previously noted, ETV is a synthetic analogue of guanosine. It is slightly soluble in water. No concerns regarding the CMC data were raised during the review cycle. The manufacturing sites were inspected prior to this approval and no significant concerns were raised.

3.2 Animal Pharmacology/Toxicology

The pharmacokinetic (PK) characteristics of ETV 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 central nervous system 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 was likely of little relevance to human safety but would need to be evaluated. 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 with long-term ETV compared to historical control animals.

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 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) studies. These studies are reviewed in detail by our Clinical Pharmacology/Biopharmaceutics Reviewer, Dr. Kim Bergman.

Table 4.2A: 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	Randomized (1:1), double blind study, 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	Randomized (1:1), double blind study, 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	Randomized (1:1:1:1), double blind study, 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	Randomized (1:1), double blind study, 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
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	9	ETV 1 mg for 48 weeks, 48 week extension	HBV DNA by bDNA and PCR assays

	LVD or HBIG			
AI463038 Worldwide	HIV/HBV coinfected 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
AI463012 China	Non-IND, randomized (1:1), double blind study Nucleoside-naïve, HBeAg positive or negative	212 (204 received open-label ETV)	ETV 0.1 mg or 0.5 mg or placebo for 28 days, followed by 56 day wash-out period, followed by open-label ETV 0.5 mg for 48 weeks	Virologic, serologic, and biochemical
AI463056 China	Non-IND, randomized (4:1), double blind study LVD-refractory, HBeAg positive or negative	145	ETV 1 mg QD or placebo for 12 weeks followed by open-label ETV 1 mg for 36 weeks (only blinded portion of study submitted)	Virologic, serologic, and biochemical

Source: Adapted from NDA 21-797, Summary of Clinical Safety, Volume 7, Table 1.1.2A, pages 31-35.

4.3 Review Strategy

The Clinical Review of NDA 21-797 was conducted by two Medical Officers (Drs. Linda Lewis and Yoshihiko Murata) working in parallel to assess data from the 4 pivotal trials and supportive studies in key populations. As the primary clinical reviewer, Dr. Lewis coordinated integration of the reviews and was responsible for writing this report. The Clinical Review was complemented by a Statistical Review of primary and secondary efficacy endpoint analyses and sensitivity analyses and subgroup analyses for the pivotal trials conducted by Dr. Tom Hammerstrom, Mathematical Statistics Reviewer. Review of the efficacy and safety data was conducted for individual studies and for the pooled nucleoside-naïve population (Studies 022 and 027) and pooled LVD-refractory population (Study 026 and relevant treatment groups of Study 014). Studies 015 (in post-liver transplant subjects) and 038 (in HIV/HBV co-infected subjects) were evaluated separately since they were small studies involving specialized study populations that might have different efficacy and safety profiles. The Phase 2 Studies 004 and 005 were reviewed for dose-response (efficacy and safety) by the Clinical Pharmacology Reviewer. Studies 007 and 901, the rollover protocols, were not reviewed in detail for this NDA. This review integrates the findings and reports of the two Medical Officers and will summarize findings of the reviewers from other disciplines.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to perform site investigations on representative study sites. Because of the large number of sites and investigators and the relatively small number of subjects enrolled in the clinical trials at each site, a small proportion of sites, investigators, and enrolled subjects were audited. A list of selected sites and principal investigators who contributed the largest numbers of subjects to the pivotal clinical trials was provided to DSI. One of the selected investigators enrolled subjects in all 4 of the pivotal trials while others enrolled in 2 or 3 trials. These pivotal studies were conducted predominately in non-U.S. sites. Individual sites in the U.S., Canada, and Europe enrolled fewer than 10 patients in any study. From the list of most active sites, the DSI staff selected 4 investigators/sites to audit: one in Taiwan, one in the Phillipines, and 2 in Turkey. Final reports of the audits confirm that no significant deficiencies were identified at any of the 4 sites inspected, the data reviewed was acceptable, and no subsequent follow-up inspections were needed.

4.5 Compliance with Good Clinical Practices

The applicant states that clinical studies were carried out in compliance with Good Clinical Practice standards. Informed Consent was obtained from all participants in the clinical trials. The Informed Consent forms for the pivotal clinical trials were reviewed by this Medical Officer prior to study initiation. After review of the animal carcinogenicity study results, the Informed Consent forms were amended to include the potential risk posed by these findings.

4.6 Financial Disclosures

The applicant included in the NDA submission signed FDA Form 3454 for the submitted studies. FDA Form 3455 was filed for 2 investigators participating in the ETV clinical development program. The financial disclosures for these 2 investigators are described below.

- — reported that he owned 1439 shares of BMS common stock. — was a subinvestigator at one of the sites participating in several of the ETV Phase 1 studies (. The reported disclosure was in relation to Study which — provided backup coverage for the Principal Investigator and was believed not to result in any bias to the study data.

- — reported that he was the recipient of a 5-year BMS Unrestricted Infectious Disease Research Grant totaling $500,000. The grant commenced on , and is being paid to the — over 5 years in yearly increments of $100,000. The grant is to support studies in the field of infectious disease research involving the natural history of HBV, specifically the importance of low level HBV viremia and cccDNA. — was the Principal Investigator at his site —) and enrolled subjects in several Phase 2 and 3 studies (—). The site directed by — enrolled approximately 3% of the subjects randomized for these studies. Of these, Studies —

studies. For some of the earlier Phase 2 studies, subjects were enrolled prior to awarding of the grant. It was concluded that — participation in the studies did not result in any bias to the study data.

After review of the above information, it was concluded that participation of these investigators in the studies had no significant effect on the studies' integrity and would not have an impact on the conclusions of the data review.

5 CLINICAL PHARMACOLOGY

For a complete review of the clinical pharmacology studies submitted with this NDA and the FDA's interpretation of these studies, refer to the Clinical Pharmacology Reviews conducted by Drs. Kim Bergman and Jenny H. Zheng. Dr. Bergman provided the primary clinical pharmacology review and Dr. Zheng assisted with the review of the population PK/PD modeling and of ETV exposure in subjects with renal impairment. A summary of their findings is included below.

5.1 Pharmacokinetics

The applicant provided a comprehensive assessment of the pharmacokinetic (PK) profile of ETV including assessment of absorption, distribution, metabolism, and excretion. An integrated summary of ETV single and multiple dose PK parameters following administration of the proposed therapeutic doses (0.5 mg and 1 mg) in the fasted state are presented in Table 5.1A.

Table 5.1A: Summary Pharmacokinetic Parameters for Entecavir

Dose (mg)	Day	C_{max} (ng/mL)	T_{max}[a] (hr)	AUC[b] (ng•h/mL)	$t_{½}$ (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 Day 14

Following the administration of ETV at the to-be-marketed 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 is readily absorbed after ingestion. Food effect assessment showed that ETV exposure decreased by approximately 20% following a high-fat or light meal compared to fasted conditions. For this reason, 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. Renal excretion of unchanged drug is the primary route of ETV elimination, while biliary excretion plays a minor role. Following administration of a 1 mg dose of radioactive labeled-ETV, 75% of the total radioactivity administered was recovered in the urine and 6% was recovered in the feces. 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.

As noted above, ETV is not significantly metabolized in the liver. Several *in vitro* studies indicate that ETV is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. No oxidative metabolites of ETV were detected in urine after dosing indicating that CYP450 does not play a role in the metabolic clearance of ETV *in vivo*. Also, ETV is not a substrate for the transporter P-glycoprotein.

Patients with hepatic and renal impairment were evaluated in PK studies. As might be expected from the route of metabolism and excretion, the patients with hepatic impairment do not require dose adjustment for ETV. Patients with renal impairment, however, require significant dose adjustment. Recommendations for dose adjustment in patients with creatinine clearance < 50 mL/min were determined by modeling and simulation.

There were no significant pharmacokinetic interactions between ETV and LVD, ADV, or tenofovir in Phase 1 drug interaction studies. In addition, *in vitro* evaluation 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.

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 (mixed Caucasian and black/African American). Weight-normalized CL/F values were comparable between the Japanese and non-Asian study populations, suggesting the racial 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 considered most likely related to differences in renal function. No significant gender-related differences in ETV PK profile were observed. No differences in doses are recommended based on race, age, or gender.

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-liver transplant, 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 transplant recipients was consistent with the degree of renal impairment in these subjects.

5.2 Pharmacodynamics

Pharmacodynamic (PD) relationships between ETV exposure and changes in HBV DNA were the basis for determining the extent of antiviral activity in the Phase 2 studies. In the population PK/PD analysis of Phase 2 data from pooled Studies AI463004, AI463005, and AI463014, change in viral load over time was well described by a direct effect inhibitory maximum effect (Emax) model. Subjects with greater exposure (dose or steady state AUC) had faster and greater maximal reductions in HBV DNA. This PK/PD relationship is described for the key Phase 2 studies in Section 5.3 Exposure-Response Relationships.

In the applicant's population PK/PD analysis of Phase 2 data from Studies 004, 005, and 014, no clear relationships between the doses administered and the severity of pooled adverse events were observed, specifically for CNS and GI events. Similarly, no relationship between predicted ETV exposure (Cmax, AUC, or Cmin) from the population model and the severity of headache or selected CNS (headache, photophobia, blurred vision, somnolence, lethargy, and dizziness) or GI (nausea, vomiting, and dyspepsia) adverse events was observed.

Based on the lack of signal from *in vitro* and animal studies, no effects on QT interval were anticipated with ETV use and a definitive QT study was not conducted. This approach was discussed with the Review Team and was considered acceptable. A brief description of the PK/PD relationship between drug exposure and selected ECG parameters is presented in Section 5.3.

5.3 Exposure-Response Relationships

Exposure-response analyses of HBV DNA changes and safety parameters in the Phase 2 studies were used to select the doses of ETV to be carried forward in the Phase 3 studies.

In the double-blind, randomized, placebo-controlled, pilot Study AI463004 investigating a range of entecavir doses (0.05, 0.1, 0.5, and 1 mg once daily for 28 days) in adults with chronic HBV infection (mixed nucleoside-naïve and LVD-refractory subjects), all ETV doses studied exhibited significant antiviral activity compared to placebo following 28 days of treatment. At 8

weeks (4 weeks post-dosing period), the two higher ETV doses of 0.5 and 1 mg were associated with significantly greater viral suppression than the lower doses suggestive of sustained antiviral activity.

A dose-response relationship was also demonstrated in the double-blind, randomized Study AI463005 investigating a range of ETV doses (0.05, 0.1, and 0.5 mg once daily for 24 weeks) compared to LVD (100 mg QD) in adults with chronic HBV infection with well-compensated liver disease. The 0.1 and 0.5 mg doses of ETV, with 4.31 and 4.72 $\log_{10}$ reductions in HBV DNA, respectively, displayed greater activity than the 0.01 mg dose. Reduction of HBV DNA by PCR was significantly greater following 22 weeks of 0.5 mg ETV QD versus the 0.1 mg dose.

In the double-blind, randomized, Study AI463014, three doses of ETV (0.1, 0.5, and 1 mg once daily for 24 weeks) were investigated in subjects with chronic HBV infection with viremia while treated with LVD. The dose response for ETV in this LVD-refractory population was also evident based on HBV viral load reductions during treatment. A linear regression model applied to the reduction from baseline in HBV DNA by PCR assay showed a significant dose response over the dose range of 0.1 to 1 mg and ETV 1 mg was superior to 0.5 mg for the primary endpoint, HBV DNA < LOQ by bDNA assay at Week 24.

An integrated summary of safety data from the Phase 1 studies evaluating doses of ETV from 0.05 mg to 40 mg suggested that the rates of all AEs increased with increasing dose. Two of the more commonly reported AEs, headache and nausea, were more common at the higher doses. In the Phase 2 studies, pooled nervous system/neurologic AEs were documented more frequently at the highest doses (1 mg in Study 004 and 0.5 mg in Study 005). In Study 005, there was a distinct dose-related increase in pooled neurologic AEs across the ETV dose levels. These finding were not observed in Study 014, the dose-ranging study in LVD-refractory subjects.

Based on consideration of these virologic and safety data, the applicant proposed further Phase 3 testing of doses of ETV 0.5 mg once daily in the nucleoside-naïve population and ETV 1 mg once daily in the LVD-refractory population. Dose selection for the Phase 3 studies was discussed at an End-of-Phase-2 meeting and the Review Team agreed with the applicant's proposed doses.

To further define the potential for ETV to cause untoward cardiac effects, a retrospective analysis (Study AI463041) of ECGs collected in five Phase 1 randomized single and multiple dose studies of ETV (AI463001, AI463002, AI463010, AI463033, and AI463034) was conducted. These studies evaluated single and multiple doses of ETV administered over the proposed therapeutic dose range (0.5 and 1 mg), and at doses significantly higher than the proposed therapeutic doses (up to 40 mg). The primary objective of the retrospective ECG analysis was to assess the effect of ETV on the QT interval corrected for heart rate using Bazett's formula (QTcB). Secondary and tertiary objectives included assessing the effect of ETV on QT interval corrected for heart rate using Fridericia's formula (QTcF), PR, RR, the relationship between the QT and RR, QRS, absolute QT, and heart rate.

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. The slight prolongation in PR in this retrospective analysis is not expected to be clinically significant but additional analysis of a wider spectrum of study participants has been requested to verify these findings.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Treatment of Chronic HBV

The indication being sought for ETV is for the treatment of chronic HBV infection in adults with evidence of The applicant asks that the indication apply to the different HBV sub-populations evaluated in the clinical trials: hepatitis B e antigen (HBeAg) positive patients, HBeAg negative patients, nucleoside-naïve patients, patients who received prior IFN therapy, LVD-refractory patients, and patients with HIV/HBV co-infection.

6.1.1 Methods

Data from the 3 Phase 3 studies were used in the primary efficacy review to support the proposed indication. These studies all evaluated the treatment effects of ETV compared to LVD on the primary efficacy endpoint, improvement in liver histology after 48 weeks of dosing, and on a variety of secondary virologic, serologic, biochemical, and composite efficacy endpoints. Study 022 evaluated the nucleoside-naïve, HBeAg positive population. Study 027 evaluated the nucleoside-naïve, HBeAg negative population. Study 026 evaluated the LVD-refractory, HBeAg positive population. In addition, virologic, serologic, biochemical, and composite efficacy endpoints were evaluated in Study 014 to support the primary efficacy analysis in the LVD-refractory population (HBeAg positive or negative). Study 038 evaluated virologic, serologic, and biochemical efficacy endpoints after 24 weeks of ETV treatment in a population of HIV/HBV co-infected subjects. In all of the primary and supportive studies, subjects were allowed to have received prior IFN therapy. Please refer back to Section 4.1, Table 1 for descriptions of the clinical trials submitted in the NDA.

6.1.2 General Discussion of Endpoints

Historically, the Division of Antiviral Drug Products (DAVDP) has required histologic endpoints in the analysis of efficacy of drugs for treatment of chronic HBV. Improvement in liver histology is considered a surrogate for the true endpoints, development of HBV-related complications (cirrhosis, liver transplantation, hepatocellular carcinoma) and death. At the time of the approval of ADV in August, 2002, DAVDP convened an issue-oriented Advisory Committee to discuss the design of clinical trials of HBV and the appropriate efficacy endpoints to be considered for drug approval. At that time, extensive statistical evaluation of data

generated during the LVD and ADV clinical trials was presented. These data showed very poor capacity of virologic (HBV DNA levels) and biochemical (ALT levels) endpoints to predict improvement in liver histology after 48 weeks of treatment. The decision of the Advisory Committee was that liver histology was still the gold-standard for approval of drugs for HBV. However, the limitations of liver biopsy were identified including: risks of the procedure, subjects' hesitation to undergo the procedure, difficulty in obtaining an adequate and representative sample of liver tissue, and limitations on the number of time-points at which samples can be obtained.

Liver histology can be described using different grading scales which assess levels of inflammation, necrosis, and fibrosis. Two of the scoring systems most commonly used by clinical pathologists and hepatologists include the Knodell histologic activity index which rates necrosis and inflammation on an 18-point scale and fibrosis on a 4-point scale and the Ishak fibrosis score which rates fibrosis on a 6-point scale.

The primary efficacy endpoint chosen for the ETV Phase 3 studies was similar to that used in the development program for ADV and was considered appropriate. Improvement in liver histology was defined in all studies as ≥ 2 point decrease in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score at Week 48 compared to baseline. In order to decrease subjectivity in scoring the histology, all biopsies were evaluated by a central pathologist who remained blinded to the subjects' treatment and the temporal order of the biopsies. The pathologist who scored the biopsies for the ETV studies was the same pathologist who evaluated biopsies performed for the ADV clinical trials.

Multiple supporting secondary endpoints are considered appropriate for anti-HBV drug assessment. Among the most widely used are measurements of circulating HBV DNA, measurements of hepatitis B e antigen (HBeAg) and anti-e antigen antibody (HBeAb), and measurements of liver aminotransferases (ALT and AST). All of the pivotal studies used 2 assays to measure changes in HBV DNA: HBV DNA using a branched DNA hybridization assay (Chiron/Bayer Quantiplex™ v1.0) with a lower limit of quantitation (LOQ) of 0.7 MEq/mL and HBV DNA using a PCR assay (Roche COBAS Amplicor HBV Monitor™ v2.0) with an LOQ of 300 copies/mL. 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.

6.1.3 Study Design

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 (for more detailed review of Phase 2 studies, refer to Dr. Bergman's Clinical Pharmacology Review). 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 0.01 mg, 0.1 mg, or LVD 100 mg. In these Phase 2 studies (especially Study 005), there appeared to be a dose-response relationship between ETV

dose and some pooled neurologic adverse events (AEs). Safety and tolerability of ETV 0.5 mg was suggested to be 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 efficacy 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 < LOQ by bDNA. In this study, there were no observed differences in safety and tolerability across the treatment arms and no observed dose-response relationship for any AEs. Consequently, ETV 1 mg was carried forward into the Phase 3 study in LVD-refractory patients (Study 026).

Decisions regarding dose-selection were discussed with the Review Team at the End-of-Phase 2 meeting. The Phase 2 dose-finding studies were considered appropriate. Doses to be further evaluated in the Phase 3 studies were acceptable based on the pharmacologic, virologic, and clinical data available.

The Phase 3 studies of ETV utilized similar study designs and endpoint analyses for assessing different sub-populations of adults with chronic HBV. For details of study design, please refer to the individual study reviews included in the Section 10, Appendix of this review. All studies used techniques intended to minimize bias: randomization of subjects, blinding, pre-specified primary and secondary endpoints, use of a single, blinded pathologist evaluating liver biopsies, and a prospectively agreed upon statistical analysis plan. All of the studies used the same, active control, LVD 100 mg, the only approved oral therapy for chronic HBV at the time the studies were initiated.

Study 022 was a randomized, double-blind comparison of ETV 0.5 mg versus LVD 100 mg in HBeAg-positive, nucleoside-naïve subjects with compensated liver function. Other key inclusion criteria included: age > 16 years, ALT > 1.3 x ULN, normal renal function, and compensated liver disease. Previous treatment with IFN was not an exclusion. Female subjects were not allowed to be pregnant or breastfeeding and appropriate contraception was required of all participants. Study subjects were followed monthly for safety monitoring. 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 $\geq$ 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 $\geq$ 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, proportion of subjects who achieved HBV DNA below the LOQ of the assays, normalization of

ALT, HBeAg loss, HBeAg/HBeAb seroconversion, and various composite endpoints. Durability of the Complete Response was evaluated in the eligible subgroup at the end of 24 weeks of off-treatment follow-up.

Study 027 was a randomized, double-blind comparison of ETV 0.5 mg versus LVD 100 mg in HBeAg-negative, nucleoside-naïve subjects with compensated liver function. Inclusion criteria were similar to those in Study 022 except for HBeAg status. Study design was similar to Study 022 with similar management decisions occurring at Week 52. In the treatment management algorithm, subjects achieving < 0.7 MEq/mL HBV DNA by bDNA assay and ALT < 1.25 x 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 and secondary endpoints were similar to those in Study 022 except that HBeAg loss and HBeAb seroconversion were not evaluated in this population. Durability of the Composite Response was evaluated in the eligible subgroup at the end of 24 weeks of off-treatment follow-up.

Study 026 was a randomized, double-blind comparison of ETV 1 mg versus LVD 100 mg in HBeAg-positive, LVD-refractory subjects with compensated liver function. Subjects were randomized to either continue LVD or receive ETV without a washout period. Continuation of treatment at the end of 52 weeks was based on results of the Week 48 evaluation. Criteria for continuation of blinded therapy through 96 weeks were based on Complete, Partial, or Non-Response and were similar to those in 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 x ULN). Multiple secondary endpoints were evaluated as in the other studies. Durability of the Complete Response was evaluated in the eligible subgroup at the end of 24 weeks of off-treatment follow-up.

The Phase 3 studies were determined to meet the FDA criteria of adequate and well-controlled clinical trials using appropriate endpoints and efficacy analyses. Entry criteria for the 3 studies were considered appropriate and they enrolled 3 important sub-populations of patients with chronic HBV. In addition, the smaller Study 038 provided non-histologic efficacy data for another important subgroup, patients with HIV/HBV co-infection. The studies were of sufficient duration to make valid efficacy conclusions. The populations studied represented the spectrum of HBV-infected patients with compensated liver disease and should allow generalization of the study results to a broader population. The studies submitted do not adequately address the response to ETV treatment of patients with decompensated liver disease or those who are post-liver transplant.

6.1.4 Efficacy Findings

Subjects 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

subjects 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. In all of the ETV pivotal studies there were very few black/African American subjects enrolled, approximately 2% across the studies. This significantly under-represents this group in the clinical trials compared to an increased prevalence of chronic HBV in African Americans in the U.S. population.

Table 6.1.4A: Subject 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%

Source: Medical Officers' review of the electronic datasets.
*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 6.1.4B: 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 necroinflammatory score	7.8	7.9	ND	6.5
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%	68%	97%
HB e antibody positive	3%	99%	28%	4%

Source: Medical Officers' review of the electronic datasets.
ND, not done

For a complete review of the primary efficacy analysis and selected secondary analyses please see the Statistical Review conducted by Dr. Tom Hammerstrom. The discussion of efficacy included below is derived from his analyses, additional calculations performed by the Medical Officers reviewing individual and pooled study data, and the applicant's stated results in the

initial NDA material and the Safety Update containing updated efficacy data for Study 027 submitted later in the review cycle.

Primary Efficacy Analysis

The primary efficacy endpoint for the Phase 3 studies was histologic improvement in the Week 48 liver biopsy compared to the baseline biopsy. Histologic improvement was defined as ≥ 2 point improvement in Knodell necroinflammatory score with no worsening in the Knodell fibrosis score. The applicant used as their primary analysis a modified ITT analysis that evaluated only subjects who had an adequate baseline biopsy with a Knodell necroinflammatory score ≥ 2 and counted subjects with a missing or inadequate Week 48 biopsy as treatment failures. The efficacy analyses were planned as a two-step process with an analysis of non-inferiority of the 2 treatment arms to be completed first. If ETV proved to be non-inferior, a second step analysis was planned to evaluate superiority of ETV compared to LVD.

The FDA statistical analysis confirmed the applicant's analyses of the primary efficacy endpoint. Although the studies were originally designed to show non-inferiority of ETV to LVD, the analysis demonstrated that a significantly greater proportion of subjects receiving ETV experienced overall histologic improvement compared to LVD in all 3 studies as shown in Table 6.1.4C (p values ≤ 0.02 in all studies). ETV was superior 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.

Table 6.1.4C: 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%
Missing baseline biopsy	11%	12%	9%	8%	12%	21%
Missing or inadequate biopsy at Week 48	6%	13%	10%	12%	10%	12%

Source: FDA Statistical Review.
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 evaluable baseline biopsy, with missing Week 48 biopsy = failure.
#ETV significantly better than LVD, va P lues all < 0.03.

The Statistical Reviewer performed a series of sensitivity analyses in evaluating the primary efficacy endpoint of overall histologic improvement. These analyses used different methods to impute missing data for each of the Phase 3 studies, 2 of which are displayed in Table 6.1.4D in comparison to the applicant's primary analysis. In FDA sensitivity analysis C, subjects with missing or inadequate baseline or Week 48 biopsies were excluded from the analysis. In this analysis, the effect of treatment in Study 022 is similar for ETV and LVD because more subjects in the LVD arm were excluded. The treatment benefit of ETV remains evident for the other 2 studies. In FDA sensitivity analysis D, all treated subjects were included and those with missing or inadequate Week 48 biopsies were counted as treatment failures. In this analysis, a greater proportion of ETV-treated subjects achieved the primary histologic endpoint compared to LVD-treated subjects. These represent more conservative analyses than the applicant's primary analysis and the treatment benefit of ETV remains.

Table 6.1.4D: Sensitivity Analyses of Primary Efficacy Endpoint at Week 48

	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
Overall histologic improvement	72%*	62%	70%*	61%	55%*	28%
FDA sensitivity analysis C	77%	72%	78%*	70%	62%*	33%
FDA sensitivity analysis D	64%*	55%	64%*	56%	48%*	22%

Source: FDA Statistical Review.
*ETV significantly better than LVD, $p < 0.05$.

The FDA statistical reviewer also performed a series of subgroup analyses based on demographic and baseline disease characteristics. The treatment effect for the primary endpoint was comparable for the covariates: gender, race, age, geographic region, HBV subtype, baseline ALT, baseline HBV DNA by bDNA or PCR assay, and prior IFN or LVD treatment.

Secondary Efficacy Analyses

Treatment effects of ETV compared to LVD were also assessed for a number of secondary endpoints using histologic, virologic, serologic, and biochemical measurements. FDA statistical review analyses confirmed the applicant's results for the following secondary endpoints: proportion of subjects with improvement in Ishak fibrosis score at Week 48, proportion of subjects with HBV DNA below 400 copies/mL 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) as shown in Table 6.1.4E.

ETV was equivalent (non-inferior) to LVD for the secondary histologic endpoint of improvement in Ishak fibrosis score in the nucleoside-naïve subjects but was superior in the

LVD-refractory population. The secondary analyses verify that ETV provides superior virologic suppression of HBV compared to LVD at 48 weeks of study dosing as measured by either the HBV DNA bDNA assay or the HBV DNA PCR assay in all 3 pivotal studies. Subjects receiving ETV experienced a greater decrease in mean HBV DNA by PCR than did those receiving LVD. Similarly, while the majority of subjects achieved normalization of ALT over 48 weeks, the subjects receiving ETV achieved this endpoint more frequently. ETV-treated subjects achieved normalization of ALT more often than LVD-treated subjects regardless of whether normalization was defined as < 1.25 x ULN (the applicant's analysis) or < 1.0 x ULN (the FDA analysis). In all analyses, the treatment difference between ETV and LVD was greatest in LVD-refractory subjects (Study 026)

Table 6.1.4E: Selected Secondary Histologic, Virologic, Serologic, and Biochemical Efficacy Endpoints

	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
Improvement in Ishak score at Week 48	39%	35%	36%	38%	34%[§]	16%
HBV DNA by PCR < 400 copies/mL	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
*HBeAg seroconversion defined as loss of e antigen with gain of e antibody.
[#]ETV significantly better than LVD, $p < 0.01$.
[§]ETV significantly better than LVD, $p < 0.05$.

Sensitivity analyses were also conducted for the secondary histologic endpoint and supported the conclusion that ETV was no worse than LVD as measured by the Ishak score. More limited subgroup analyses were performed to assess some of the secondary endpoints. The treatment effect measured as proportion of subjects with ALT normalization and HBV DNA < 400 copies/mL at Week 24 or 48 was similar according to: gender, race, and age.

Among 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 in Study 022, only 9% of ETV patients and <1% of LVD patients reached the Complete Response endpoint.

The applicant also evaluated the durability of these protocol-defined treatment responses. A sustained response was defined as sustaining the study Complete or Composite Response parameters through the 24 week off-treatment follow-up period. The proportion of subjects with sustained response was different in the populations studied in the 3 pivotal trials. Among Responders in Study 022, 61/74 (82%) ETV subjects and 49/67 (73%) LVD subjects sustained the Complete Response criteria through 24 weeks of off-treatment follow-up. In Study 026, very few subjects were eligible to discontinue treatment on the basis of achieving a Complete Response; 5/13 ETV subjects and 1/1 LVD subjects were able to sustain this response through 24 weeks off-treatment. In Study 027 a greater proportion of subjects entered the off-treatment follow-up but only 124/259 (48%) ETV subjects compared to 78/220 (35%) LVD subjects maintained the Composite Response criteria. An exploratory analysis of the Composite Response cohort identified that 96% of ETV subjects and 85% of LVD subjects achieved HBV DNA by PCR < 400 copies/mL at the end of study dosing. However, at the end of off-treatment follow-up, only 4% of ETV subjects and 3% of LVD subjects maintained this level of HBV DNA suppression. In the nucleoside-naïve, HBeAg negative population, the protocol-defined response criteria failed to reliably identify a subgroup who could sustain the specified virologic and biochemical response.

Efficacy in Special Populations

The use of ETV as treatment for chronic HIV/HBV was evaluated in some of the key special populations: HIV/HBV co-infected subjects (Study 038), post-liver transplant subjects (Study 015), and subjects with decompensated liver disease (Study 048). Study 048 comparing treatment with ETV to ADV is currently still enrolling and there were insufficient data to conduct an interim analysis for efficacy during this review cycle. Studies 015 and 038 were reviewed as supportive studies (see Section 10.1 Appendices for individual study reviews).

The interim study report for Study 038 submitted with this NDA contains the 24-week efficacy and safety data. At the time of the report, this study was ongoing at 28 international sites. This was a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of ETV in HIV/HBV co-infected subjects for 24 weeks during the blinded phase followed by open-label administration of ETV for an additional 24 weeks. A total of 68 subjects on stable, LVD-containing antiretroviral therapy were randomized 2:1 to receive ETV 1.0 mg or placebo QD. Because 22 out of 24 sites randomized fewer than six subjects per site (i.e. the block size for the protocol-specified 2:1 randomization scheme), the final ETV: placebo ratio was nearly 3:1. All eligible subjects were to continue their ongoing LVD therapy (as 150 mg BID or 300 mg QD) throughout the study. During the course of the study, HBV DNA levels, HBV serologies, HIV RNA levels, CD4 cell count, and clinical and laboratory safety assessments were taken at

specified intervals. Following the conclusion of the first 24 week period during which the study drug was administered in a double-blind manner, all subjects continued study participation into the 24 week open-label phase in which ETV 1.0 mg QD was administered to all subjects. Following the completion of the open-label phase, all subjects were given the opportunity to continue open-label administration of ETV.

In Study 038, the primary efficacy endpoint was the mean HBV DNA level by PCR at Week 24, based on a linear regression model adjusted for baseline HBV DNA level. A number of secondary efficacy endpoints were also examined, including the proportion of subjects with HBV DNA < 400 copies/mL at Week 24, mean HBV DNA level at Week 48, proportion of subjects with ALT normalization (defined as ALT < 1.25 x ULN) at Weeks 24 and 48, HBV DNA mutations during the course of the study, and the proportion of subjects with HBe seroconversion. Liver histology was not evaluated in this study.

Of the 68 subjects enrolled, most completed the blinded treatment phase (94% ETV subjects, 100% placebo subjects, all of whom received ETV in the open-label phase of the study). The majority of the treated subjects were male (96%) and Caucasian (85%) and their mean age was 41 years. Approximately 50% of subjects were from South America, while the remaining subjects were from Europe (35%) and North America (15%). In general, the treatment arms were balanced with respect to demographic characteristics and baseline HIV and HBV characteristics.

At Week 24, the mean HBV DNA levels for ETV and PLB groups were 5.52 and 9.27 $\log_{10}$ copies/mL, respectively. The estimated difference, when adjusted for baseline levels, in the reduction of mean HBV DNA levels (ETV – PLB) was -3.76 $\log_{10}$ copies/mL (95% CI: [-4.5, -3.0]; $p < 0.0001$). Although these results are encouraging, only 3 ETV subjects (6%) and no PLB subjects achieved HBV DNA levels < 400 copies/mL at Week 24. HBeAg loss and seroconversion at Week 24 occurred in one subject in the ETV arm and none in the PLB group. The applicant notes that ALT normalization (< 1.25 x ULN) occurred in 11/30 (37%) subjects treated with ETV compared to 1/7 (14%) receiving PLB (among subjects who had baseline ALT levels ≥ 1.25 x ULN). These efficacy results were confirmed by the FDA Statistical Reviewer.

Study 015 was a small, open-label, pilot study conducted to evaluate ETV 1 mg daily in subjects who had received orthotopic liver transplant and had recurrent HBV in spite of anti-HBV prophylaxis. Subjects enrolled in this study were required to be clinically stable, at least 100 days post-transplant, on stable doses of cyclosporine or tacrolimus, and have documentation of recurrent HBV viremia despite post-transplant prophylaxis with any agents active against HBV (HBV immune globulin, LVD, ADV, famciclovir, emtricitabine, ganciclovir or a combination of these drugs). The study assessed response to treatment at Weeks 12, 24, and 48. Subjects who failed to achieve ≥ 1 log decrease in HBV DNA by bDNA assay at Week 12 or who had detectable HBV DNA by bDNA (> 0.7 MEq/mL) at Week 24 could elect to discontinue ETV treatment. Subjects with undetectable HBV DNA by bDNA at study evaluations at Weeks 24, 48, and 96 could continue dosing with ETV. HBV isolates were evaluated for emergence of resistance mutations associated with LVD and ETV at baseline and throughout the study.

Pharmacokinetic assessment of ETV was performed on the first day of dosing and at steady state (Day 14).

In this small study, the primary objectives were to assess the safety and PK profile of ETV in liver transplant subjects. Multiple evaluations of efficacy were included as secondary objectives. Efficacy endpoints included: the proportion of subjects who achieved undetectable HBV DNA by bDNA (< 0.7 MEq/mL), the proportion of subjects who achieved HBV DNA by PCR < 400 copies/mL, the proportion of subjects who achieved > 1 log decrease and > 2 log decrease in HBV DNA, the proportion of subjects with undetectable HBsAg and HBeAg and seroconversion, and the proportion of subjects with normalization of ALT (< 1.25 x ULN) or 50% improvement in ALT. The endpoints were evaluated at Week 24 and the proportion of subjects who maintained each endpoint at Week 48 was determined. Although liver biopsies were not required, they were encouraged at baseline, and Weeks 24 and 48 and changes in liver histology were to be assessed if possible.

This study enrolled only 9 subjects, of whom 6 were white, 8 were male, 6 were North American, and the average age was 53 years. Five subjects were HBeAg positive. At baseline the median log HBV DNA by bDNA was 2.9 log, median log HBV DNA by PCR was 8.6 log, and median ALT level was 71 IU. The median duration of ETV therapy in this group was 129 weeks.

In this small cohort of liver transplant recipients, HBV DNA as measured by the PCR assay decreased by a mean 3.62 log at Week 24 and 3.90 log at Week 48. None of these subjects achieved HBV DNA < 400 copies/mL at Weeks 24 or 48. Among subjects who had abnormal ALT at baseline, all 6 achieved either ALT < 1.25 x ULN or > 50% decrease from baseline at Week 24 and 5 maintained this level at Week 48. One of 5 subjects who was HBeAg positive seroconverted at Week 24 and maintained this status throughout the study. One subject achieved HBV DNA < 400 copies/mL late in study dosing (Week 112) and later achieved HBe seroconversion and loss of HBsAg. Four of the 9 subjects had liver biopsies obtained during study treatment. Three of these subjects met the criteria for overall histologic improvement used in the pivotal studies, 2 at Week 24 and one at Week 84. Although these results are encouraging, the number of subjects evaluated in this study is too small to make any definitive conclusions regarding the effectiveness of ETV in treatment of post-liver transplant subjects.

Overall, in the 3 Phase 3 studies, a greater proportion of ETV-treated subjects achieved histologic improvement after 48 weeks of treatment compared to LVD-treated subjects. ETV also provided superior virologic suppression of HBV replication compared to LVD as measured by 2 HBV DNA assays and a greater proportion of subjects achieved normalization of ALT. Not surprisingly, these treatment differences were greater in LVD-refractory subjects than in nucleoside-naïve subjects. In a supportive study of another LVD-refractory group, ETV-treated subjects with HIV/HBV co-infection experienced better suppression of HBV replication and were more likely to normalize ALT than those receiving placebo.

To date, there have been no direct comparisons of ETV and ADV for the treatment of chronic HBV, although there is a study in progress in subjects with decompensated liver disease. The

registrational studies for ADV employed a placebo rather than active control and a different study design and, therefore, are difficult to compare to the ETV pivotal studies. However, the ADV Phase 3 studies also evaluated both HBeAg positive and HBeAg negative, nucleoside-naïve subjects and used a primary efficacy endpoint of overall histologic improvement similarly defined. The ADV product label states that 53% of HBeAg positive, nucleoside-naive subjects receiving ADV and 64% of HBeAg negative subjects receiving ADV achieved histologic improvement at Week 48 compared to 25% and 35%, respectively, of subjects receiving placebo. From these data it is impossible to conclude whether ETV will provide a treatment benefit compared to ADV.

6.1.5 Clinical Microbiology

The applicant has performed extensive evaluation both in vitro and in vivo regarding the potential for development of resistance to ETV. Subjects in the ETV clinical trials were monitored systematically for emergence of resistance in their HBV. For a complete review of the in vitro and clinical microbiology data, refer to the Clinical Microbiology Review conducted by Dr. Lisa Naeger. A summary of her conclusions is included in this review.

The efficacy of ETV was examined in both nucleoside-naive and LVD-refractory populations. In nucleoside-naïve Studies 022 (HBeAg positive subjects) and 027 (HBeAg negative subjects), approximately 83% of subjects on 0.5 mg ETV treatment were suppressed with HBV DNA < 400 copies/mL as quantified by the PCR assay at Week 48 compared to 59% of subjects on 100 mg 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 in Study 022 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 compared to LVD 100 mg in subjects with LVD-refractory HBV with prior LVD treatment 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, only 21% of subjects on ETV were suppressed to < 400 copies/mL HBV DNA by PCR assay at week 48 compared to 1% of subjects 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 was suppressed < 300 copies/mL (LOQ) in some subjects and the others experienced > 2 $\log_{10}$ 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 pilot Study 015 examined the antiviral activity of open label ETV 1 mg QD in 9 liver transplant recipients who were > 100 days post-transplant and had recurrent HBV infection. 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).

Evaluation of treatment responses to ETV and monitoring resistance to ETV beyond 48 weeks of dosing are ongoing in the clinical trials. Additional data are needed to identify the timing and path to ETV resistance, particularly in nucleoside-naïve subjects.

6.1.6 Efficacy Conclusions

The FDA Review Team concluded that in well-conducted, multinational, studies in key subgroups of patients with compensated liver function, ETV was effective in the treatment of adults with chronic HBV infection and evidence of ongoing liver inflammation. The Phase 3 studies met the FDA criteria of adequate and well-controlled studies. Analysis of the study results confirmed that ETV was superior to LVD in achieving the primary endpoint of overall histologic improvement in each of the 3 Phase 3 studies enrolling different important patient populations. Sensitivity analyses conducted by both the applicant and the FDA Statistical Reviewer supported the robustness of these results. Similarly, the treatment effect measured by the primary efficacy endpoint was observed consistently across subgroups based on gender, race, age, geographic region, and a variety of baseline disease covariates.

Review of key secondary endpoints also supported the efficacy of ETV compared to LVD. ETV was shown to be superior to LVD in all analyses evaluating changes in HBV viral load over 48 weeks regardless of which HBV DNA assay was used (bDNA or PCR). FDA review confirmed the applicant's conclusions that a greater proportion of ETV subjects than LVD subjects achieved HBV DNA < 400 copies/mL and ETV subjects achieved greater mean decreases in HBV DNA by PCR. Virologic responses were superior for ETV-treated subjects compared to LVD-treated subjects in all of the Phase 3 studies. Other key secondary endpoint analyses concluded that ETV was superior or equivalent to LVD through 48 weeks for the proportion of

subjects achieving normalization of ALT (depending on method of calculating ALT normalization and study) and the proportion with improvement in Ishak fibrosis score (depending on study).

A supportive study conducted in HIV/HBV co-infected subjects demonstrated that in patients receiving LVD as part of the HIV therapy and LVD-refractory HBV, ETV had a significant effect on HBV replication as measured by log decreases in HBV DNA levels through 24 weeks of dosing. However, only a small proportion of these co-infected subjects achieved HBV DNA < 400 copies/mL by Week 24 and a relatively small proportion achieved normalization of ALT.

There are limitations to the efficacy data presented in the ETV NDA. As noted above, the small number of blacks/African Americans enrolled in the clinical development program did not provide sufficient evidence to determine whether they respond differently to treatment with the drug. Also, although the data from the pilot study in liver transplant recipients was encouraging, the size of that study makes it difficult to draw conclusions about the efficacy of ETV in this population. There are no data submitted in the NDA regarding the efficacy of ETV in patients with decompensated liver disease due to chronic HBV infection, another important subgroup. Finally, although the results of these studies support the superiority of ETV treatment compared to LVD treatment by a variety of histologic, serologic, virologic, and composite endpoints measured at 48 weeks, there are no data comparing ETV to ADV for the treatment of chronic HBV. These areas of interest need to be investigated and will be addressed in post-marketing commitments by new or ongoing studies.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data for this NDA was provided in the form of electronic datasets containing tabulations of clinical adverse events and laboratory monitoring. Narrative summaries and case report forms were provided for all patients who died, developed serious adverse events (SAEs), or discontinued study drug because of an adverse event (AE). 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). Safety review was also conducted for the supportive studies, Study 038 in HIV/HBV co-infected subjects and Study 015 in liver transplant recipients. Results of the safety reviews for these studies are not included in the integrated safety review (for more information, refer to Section 10.1 Review of Individual Study Reports). Tabulations of AEs, SAEs, deaths, study drug discontinuations, laboratory abnormalities were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc). Some comparisons between treatment groups were made with the assistance of our Statistical Reviewer.

Safety assessment for the Phase 1 studies was performed by the Clinical Pharmacology Reviewer with assistance from the 2 Medical Officers. Please see Dr. Bergman's review for more detailed

reporting of safety in the Phase 1 and 2 program and an analysis of exposure-response for safety data. Her review also contains an analysis of the applicant's retrospective analysis from selected Phase 1 studies of QTc and PR parameters correlated with ETV exposure.

All patients who received at least one dose of blinded study medication in the pivotal trials were included in the safety analyses. This included data on 1347 nucleoside-naïve subjects (679 ETV subjects, 668 LVD subjects) and 373 LVD-refractory subjects (183 ETV subjects and 190 LVD subjects). 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 (discontinuation of study drug). Clinical events and laboratory abnormalities were evaluated according to assigned treatment (ETV or LVD) and over 2 study periods (on blinded treatment and off-treatment). 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.

In general, the safety profile of ETV was similar to that of LVD in each of the 4 pivotal studies and in pooled nucleoside-naïve subjects and LVD-refractory subjects. AEs were reported frequently in the nucleoside-naive patients (in about 81% in both arms) although there were few differences in the pattern of AEs reported by ETV-treated patients compared to LVD-treated patients. The pattern of commonly reported AEs was very similar in the LVD-refractory patients, with 85% of ETV subjects and 82% of LVD subjects reporting some AE.

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 7.1A summarizes the prevalence of common AEs and SAEs occurring in the 4 pivotal studies. More detailed description of the integrated safety review will be provided in sections to follow. For details of each specific study, refer to the individual study reports included in Section 10.1, Appendix.

Table 7.1A: 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%)

Source: Medical Officer's review of the electronic datasets.

7.1.1 Deaths

A total of 15 deaths occurred during treatment with study drugs during all of the ETV studies submitted in the NDA. 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 Phase 2 supportive studies. Causes of death included: malignancy (4 ETV, 1 LVD), liver failure (2 ETV, 2 LVD), cardiovascular/sudden death (1 ETV, 2 LVD), infection septic shock (1 ETV, 1 LVD), and multi-organ failure (1 ETV). 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 (#014-39-6039). The reviewing Medical Officers agreed with the applicant's assessments of causality based on review of the narrative summaries and CRFs provided.

Table 7.1.1A: 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	LVD 100 mg	Severe dyspnea
115-10657	Male, 64, Caucasian, Italy	395	LVD 100 mg	Diffuse metastases, prior renal carcinoma
136-10204	Female, 58, Caucasian, Brazil	239	LVD 100 mg	Grade 4 hepatic decompensation, hepato-renal syndrome
209-11016	Male, 55, Caucasian, Polish	260	LVD 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, diabetes

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 LVD-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
Supportive Studies (Study number included in Patient ID)				
004-12-10	Male, 63, Caucasian, Belgium	204	ETV 0.1 mg	Hepatocellular carcinoma, diagnosed 4 months after end of dosing
012-3-7244	Female, 19, Asian, China	201	PLB ETV 0.5 mg*	Sudden death, history of mitral valve insufficiency
056-1-60013	Male, 53, Asian,	99	PLB, ETV 1 mg**	Liver failure, hepatorenal syndrome

Source: Medical Officers' review of the electronic datasets and CRFs.
*In Study 012 (conducted in China), subjects randomized to blinded ETV or PLB (placebo) for 28 days, then off-treatment for 28 days, then received open-label ETV at 0.5 mg. This subject completed the blinded phase of the study and was receiving open-label ETV at the time of death.
In Study 056 (conducted in China), LVD-refractory subjects were randomized to blinded ETV 1 mg or PLB for 12 weeks, then all subjects were eligible to receive open-label ETV 1 mg. This subject developed progressive liver failure while receiving PLB, was unblinded, and subsequently began open-label ETV.

7.1.2 Other Serious Adverse Events

The number of patients who developed SAEs (death, hospitalization, cancer, congenital anomaly, life-threatening condition, or other medically significant event) while on study was relatively small. In the pivotal studies, the rate of on-treatment SAEs in nucleoside-naïve subjects (7% ETV, and 8% LVD) and LVD-refractory subjects (10% ETV, 7% LVD) was comparable across the treatment arms. On-treatment SAEs reported in 2 or more nucleoside-naive subjects in either treatment group are summarized in Table 7.1.2A. Among the nucleoside-naïve subjects reporting SAEs, only 1 ETV compared to 11 LVD subjects had SAEs that were considered possibly, probably, or certainly related to study drug. Seven of these subjects experienced events that included elevated liver enzymes and were Grade 3 or 4 in severity. Among LVD-refractory subjects no SAE was reported in > 2 subjects in a treatment group. Rates of SAEs were low during the off-treatment follow-up period in both the nucleoside-naïve subjects (3% ETV, 5% LVD) and the small cohort of LVD-refractory subjects who discontinued study drug per protocol (5% ETV, 10% LVD). The reviewing Medical Officers agreed with the applicant's assessments of causality based on review of the narrative summaries and CRFs provided.

Table 7.1.2A: Serious Adverse Events Occurring in ≥ 2 Subjects On-Treatment – Nucleoside-naïve

Adverse Event (MedDRA Preferred Term)	ETV (N = 679)	LVD (N = 668)
Abdominal pain (upper or not specified)	3	3
ALT increased	1	6
Benign prostatic hypertrophy	0	2
Hepatic enzyme increased	0	2
Hepatitis B	0	2
Hepatic neoplasm malignant	3	2
Kidney stones	2	1
Peritoneal hemorrhage	2	0
Post-procedural pain	2	2
Pyrexia	0	4
Road traffic accident	2	0

Source: Medical Officers' review of the electronic datasets and CRFs.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The proportions of subjects discontinuing study drug and the reasons for discontinuation differed according to study (or patient population) and year of dosing as shown in Table 7.1.3.1A below.

Only the 3 Phase 3 studies are shown since their study designs were similar and allow comparison. It should be remembered that study subjects could enter the follow-up phase at the completion of 48 weeks of dosing or at a later time and subjects could enter follow-up after being designated as a Complete/Composite Responder or as a Non-responder.

Table 7.1.3.1A: Disposition of Subjects in Entecavir Phase 3 Studies

Disposition of Subjects	Study 022		Study 027		Study 026	
	ETV	LVD	ETV	LVD	ETV	LVD
All randomized	357	358	331	317	147	146
Never dosed	3 (1%)	3 (1%)	6 (2%)	4 (1%)	6 (4%)	1 (<1%)
Received study drug	354 (99%)	355 (99%)	325 (98%)	313 (99%)	141 (96%)	145 (99%)
Did not complete first year of dosing	14 (4%)	34 (10%)	14 (4%)	17 (5%)	8 (5%)	19 (13%)
Adverse event	1	9	6	9	1	8
Death	0	2	2	0	0	1
Lost to follow-up	3	8	0	2	2	1
Noncompliance	2	4	2	2	3	1
Pregnancy	2	2	0	0	0	0
Subject no longer meets study criteria	0	4	0	0	0	1
Subject withdrew consent	6	5	4	4	2	5
Treatment failure/lack of efficacy	0	0	0	0	0	2
Completed first year of dosing	340 (96%)	321 (90%)	311 (94%)	296 (93%)	133 (90%)	126 (86%)
Continued to second year of dosing	252 (71%)	190 (54%)	46 (14%)	59 (19%)	91 (62%)	24 (16%)
Did not complete second year of dosing	18 (7%)	67 (35%)	7 (2%)	12 (4%)	13 (9%)	17 (12%)
Adverse event	0	1	0	0	1	1
Lost to follow-up	2	2	1	1	0	0
Noncompliance	1	0	2	0	0	0
Pregnancy	1	1	0	0	0	0
Subject no longer meets study criteria	0	7	4	2	1	0
Subject withdrew consent	7	2	0	0	0	1
Treatment failure/lack of efficacy	7	54	0	9	10	15
Death	0	0	0	0	1	0
Completed second year of dosing	117 (46%)	67 (35%)	31 (9%)	37 (12%)	30 (20%)	0

Entered/completed 24-week follow-up	135/81	132/77	299/235	263/148	41/15	21/11

Source: AI463022: Clinical Study Report, page 126. AI463022 Clinical Study Report Addendum 01, pages 61, 62.
AI463027: Clinical Study Report Addendum 01, pages 68, 72.
AI463026: Clinical Study Report, page

7.1.3.2 Adverse events associated with dropouts

In general, the total number of patients discontinuing their assigned study drug because of an AE or SAE was low, 11/862 (1%) ETV-treated patients and 35/858 (4%) LVD-treated patients. Among nucleoside-naïve subjects numerically fewer ETV subjects (1%) than LVD subjects (3%) discontinued study drug because of an AE. The most common AEs resulting in study drug discontinuation in this population were: increased ALT/AST (1 ETV, 6 LVD), increased amylase and/or lipase (3 ETV, 5 LVD including one exacerbation of chronic pancreatitis), and malignancy (2 ETV, 3 LVD). Discontinuations due to AEs among nucleoside-naïve subjects are tabulated in Table 7.1.3.2A.

Table 7.1.3.2A: Subjects Reporting Adverse Events Resulting in Study Drug Discontinuation – Nucleoside-Naïve

Patient ID Number	Treatment	Age/Sex/Race	Days on Study Drug	Adverse Event Resulting in Discontinuation	Relationship to Study Drug
Study 022					
9-10978	LVD	27/M/Asian	21	Pruritic rash	Probable
13-10109	LVD	40/M/White	29	Increased ALT (Grade 4)	Possible
115-10657	LVD	64/M/White	357	Metastases to CNS (death)	Not related
125-10177	LVD	32/F/ Asian	113	Pregnancy	Not related
129-10960	LVD	41/M/Asian	30	Abnormal lipase	Possible
132-10324	LVD	56/M/White	167	Elevated lipase	Certain
136-10204	LVD	58/F/White	209	Hepatic failure, renal insufficiency	Not related
152-10242	LVD	22/M/Asian	221	Increased ALT (Grade 4)	Probable
164-10598	LVD	43/M/White	64	Alcohol abuse	Not likely
183-10574	ETV	21/M/Asian	29	Increased ALT (Grade 4)	Not likely
132-10857	LVD	50/M/White	38	Elevated amylase and lipase	Not related
185-10587	LVD	29/M/White	89	Elevated ALT and AST	Possible
40-11012	LVD	44/M/Native Hawaiian-Pacific Islander	539	Elevated ALT	Possible
Study 027					
101-50558	ETV	46/M/White	309	Hepatocellular carcinoma	Not likely

112-50503	ETV	38/F/White	59	Upper abdominal pain, increased lipase and amylase	Possibly
115-50663	ETV	37/M/White	337	Increased lipase and amylase	Probably
12-50850	LVD	63/M/Asian	38	Chest pain, right lower abdominal pain, nerve compression, fatigue	Not related
121-50122	LVD	38/M/Asian	141	Increased ALT	Probably
144-50119	LVD	55/F/White	5	Dizziness, headache, flatulence	Possibly
153-51276	ETV	43/M/White	141	Increased amylase and lipase	Probably
155-50162	LVD	50/M/White	40	Exacerbation of chronic pancreatitis	Not likely
193-50490	LVD	66/F/White	357	Carcinoma in situ (breast)	Not likely
206-51097	LVD	37/M/White	283	Increased lipase	Probably
3-50963	LVD	20/M/Asian	68	Depression, suicidal ideation	Not likely
3-50976	ETV	50/F/Asian	75	Psoriasis	Possibly
40-50662	LVD	42/M/Asian	40	Hepatocellular carcinoma (transplanted)	Not related
5-50742	ETV	72/M/Asian	322	Gastric adenocarcinoma	Not related
94-50186	LVD	46/M/White	29	Increased ALT and AST	Possibly

Source: Medical Officer's review of the clinical datasets.

The rate of study drug discontinuation due to AEs was slightly higher in both treatment groups among LVD-refractory subjects. Among LVD-refractory subjects, numerically fewer ETV subjects (6/183, 3%) compared to LVD subjects (14/190, 7%) discontinued study drug because of an AE. Increased ALT or elevated LFTs accounted for 9 of the discontinuations among LVD-treated subjects and 1 ETV-treated subject. In addition, 2 LVD-treated subjects are reported to have discontinued study drug due to liver failure. One patient in each treatment group discontinued because of elevated pancreatic enzymes and one in each group discontinued because of malignancy.

Table 7.1.3.2B: Subjects Reporting Adverse Events Resulting in Study Drug Discontinuation – LVD-Refractory

Patient ID Number	Treatment	Age/Sex/Race	Days on Study Drug	Adverse Event Resulting in Discontinuation	Relationship to Study Drug
Study 026					
14-80134	LVD	49/M/Asian	330	Acute hepatitis exacerbation (SAE)	Probably
36-80002	LVD	36/M/Pacific Islander	93	Increased ALT (Grade 4)	Probably

38-80151	LVD	58/F/White	293	Skin rash	Possibly
40-80348	LVD	34/F/Asian	294	Elevated liver enzymes (Grade 4)	Possibly
50-80413	LVD	36/M/Asian	224	Elevated ALT and AST (Grade 4)	Possibly
76-80206	LVD	58/M/White	125	Elevated lipase (Grade 3)	Probably
101-80042	LVD	46/M/White	397	Hepatitis B activation/Liver failure (Death)	Not likely
101-80384	LVD	29/F/White	168	Elevated ALT (Grade 4)	Possibly
102-80125	LVD	42/M/White	217	Hepatocellular carcinoma	Not Related
109-80291	ETV	29/M/White	202	Fever, ankle arthritis, lymph node enlargement (SAE)	Not likely
125-80154	LVD	37/M/White	505	Elevated ALT and AST (Grade 4)	Possibly
131-80041	ETV	23/F/White	522	Elevated INR, PT (Grade 3)	Possibly
Study 014					
02-6240	ETV	41/M/Black	33	Elevated LFTs (Grade 3)	Probably
26-6043	ETV	42/M/White	44	Elevated amylase and lipase (Grade 3/4)	Possibly
39-6209	ETV	56/M/Black	Unknown	Chest pain (SAE)	Possibly
10-6073	ETV	65/M/White	553	Basal cell lesion	Unrelated
01-6002	LVD	46/M/White	280	Elevated LFTs (Grade 3/4)	Possibly
26-6042	LVD	40/M/White	75	Liver failure (SAE)	Not likely
26-6204	LVD	20/M/White	365	Elevated ALT (Grade 3/4)	Possibly
33-6217	LVD	66/M/White	81	Elevated LFTs (Grade 3/4)	Probably

Source: Medical Officer's review of the clinical datasets.

The assessment of whether these events were related to study drug was based on the judgment of the individual investigators. These judgments may have been somewhat subjective since the side effect profile of ETV was not well characterized at the time of the studies. However, most investigators had reasonable experience in the use of LVD for treatment of HBV and extensive experience in the complications of the underlying disease. Also, study drug use was blinded and placebo-controlled, study design techniques useful in reducing bias in assigning a relationship between study drug and a given AE.

7.1.3.3 Other significant adverse events

Some adverse events were evaluated and reported in more detail because of special significance for the review of ETV. Among these events were acute exacerbations of hepatitis or ALT flares and other significant hepatic AEs, neurologic AEs, malignancies, and lactic acidosis. A

discussion of malignancies occurring during the ETV drug development program is presented later in this review in Section 7.1.11 Human Carcinogenicity.

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 values 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: 15/679 (2%) ETV-treated subjects and 27/668 (4%) LVD-treated subjects experienced a flare. Although the numbers are small, this favors the ETV arm. 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.

In Studies 022 and 027 the study designs allowed subjects who met protocol-defined Response criteria to discontinue treatment and be followed off therapy. More subjects met the Response criteria in Study 027. For these reasons, the analysis of off-treatment ALT flares represents a selected subgroup. Compared to on-treatment, ALT flares occurred slightly more frequently in the off-treatment follow-up period in both treatment groups. Fifteen of 414 (4%) ETV subjects compared to 30/377 (8%) of LVD subjects experienced off-treatment flares. This analysis also favors the ETV arm.

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, 4/183 (2%) ETV patients and 19/190 (10%) LVD patients experienced ALT flares while receiving study drug. Six LVD patients discontinued study drug because of ALT flares.

A much smaller proportion of LVD-refractory subjects met the protocol-defined Response criteria, discontinued their therapy, and were followed off-treatment. As noted before, this represents a selected subgroup of subjects. During the off-treatment follow-up, 3/56 (5%) ETV patients and 0/31 LVD patients 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.

Nervous System/Neurologic Adverse Events

Central nervous system or neurologic AEs were identified in pre-clinical animal toxicity studies of ETV and, consequently, these events were closely monitored during early Phase 1 and 2 studies. In the Phase 2, dose-finding Study 005 in nucleoside-naïve subjects, the incidence of grouped neurologic AEs increased with increasing doses of ETV. Compared to 7% of the LVD group reporting neurologic events, 11% of subjects receiving 0.01 mg ETV, 19% of those receiving 0.1 mg ETV and 24% or those receiving 0.5 mg experienced some neurologic event. There appeared to be trends toward more frequent events of dizziness and insomnia with the 0.5 mg dose. However, in the Phase 2, LVD-refractory, dose-finding Study 014, a dose-relationship with neurologic events was not seen at doses ranging from 0.1 mg, 0.5 mg, to 1 mg ETV.

The Medical Officers searched all events categorized in the MedDRA System Organ Class as Nervous System disorders. Selected MedDRA Psychiatric disorders were included in the search if they were believed to overlap with potential central nervous system toxicity (eg., anxiety, anxiety disorder, insomnia, irritability, nervousness, and sleep disorder). These events were combined and evaluated across treatment arms and study populations. This analysis is similar in concept to the applicant's analysis of neurologic events but includes a wider variety of events. The applicant focused their evaluation on MedDRA preferred terms that were considered to reflect events related to central nervous system inflammation or vasculitis.

The safety review evaluated nervous system adverse events in the pivotal studies individually and pooled as nucleoside-naïve and LVD-refractory groups. Table X, below, displays grouped and individual neurologic adverse events from the pooled study data. Rates of all neurologic events were similar across treatment groups in both naïve and LVD-refractory subjects. The proportion of subjects reporting any neurologic event was between 32% and 36%. There were no significant differences in the proportions of subjects reporting anxiety, dizziness, headache,

insomnia, migraine, paresthesia, somnolence or syncope across treatment groups. If only subjects reporting Grade 2 to 4 (moderate to severe) neurologic events were tabulated, a slightly higher proportion of LVD-refractory subjects receiving 1 mg ETV were identified compared to LVD. This difference was accounted for by patients reporting a variety of Grade 2, moderate events. In all the primary studies, only a single subject was reported to have a Grade 4 neurologic event. No significant pattern of ETV-related neurologic AEs could be identified.

Table 7.1.3.3A: Summary of Nervous System Adverse Events in Entecavir Pivotal Studies – On Treatment

	Nucleoside-naive		LVD-Refractory	
	ETV 0.5 mg (N=679)	LVD 100 mg (N=668)	ETV 1.0 mg (N=183)	LVD 100 mg (N=190)
Number with Nervous System AEs*	227 (33%)	217 (32%)	65 (36%)	61 (32%)
Anxiety	12 (2%)	6 (<1%)	5 (3%)	5 (3%)
Dizziness	42 (6%)	39 (6%)	15 (8%)	11 (6%)
Headache	137 (20%)	128 (19%)	38 (21%)	36 (19%)
Insomnia	30 (4%)	36 (5%)	10 (5%)	12 (6%)
Irritability	4 (<1%)	3 (<1%)	1 (<1%)	2 (1%)
Migraine	5 (<1%)	5 (<1%)	3 (2%)	2 (1%)
Paresthesia	9 (1%)	10 (1%)	1 (<1%)	4 (2%)
Somnolence	10 (1%)	12 (2%)	3 (2%)	3 (2%)
Syncope or Syncope vasovagal	4 (<1%)	3 (<1%)	2 (1%)	0
Thrombotic stroke	1 (<1%)	0	0	0
Number with Nervous System AEs Grades 2-4**	62 (9%)	58 (9%)	28 (15%)	18 (9%)

*Includes all AEs designated MedDRA Nervous System Class and selected AEs desgnated Psychiatric System Class (anxiety, anxiety disorder, insomnia, irritability, nervousness, sleep disorder).
**Only one patient experienced a Grade 4 event (Study 022, LVD arm).

Lactic Acidosis

Lactic acidosis, sometimes accompanied by hepatic steatosis and/or pancreatitis, has been associated with the use of nucleoside analogue drugs in the treatment of HIV infection. The syndrome has been attributed to inhibition of mitochondrial DNA polymerase (γ polymerase). For this reason, all of the HIV nucleoside reverse transcriptase inhibitors and both LVD and ADV are labeled with a boxed warning describing the occurrence of lactic acidosis. There was no prospective evaluation conducted during the clinical trials for increased lactate or lactic acidosis. The applicant performed a retrospective search of their clinical database for events that might be related to lactic acidosis.

The applicant conducted a search of all subjects in the safety database for events that might represent lactic acidosis, hyperlactatemia, and hepatic steatosis. Each event identified was

reviewed to determine if it met the criteria of lactic acidosis syndrome. The search identified 22 subjects (11 ETV, 10 LVD, 1 placebo). Of these, the applicant states that 17 subjects had sufficient data to determine that the clinical criteria for lactic acidosis syndrome were not met. The remaining 5 subjects had insufficient laboratory data to determine their status. The applicant notes that both of the ETV-treated subjects with incomplete laboratory data experienced hepatic failure in the setting of acute renal failure and/or severe infection.

One subject enrolled in Study AI463023, a Chinese registrational study not submitted with the NDA, developed an episode of unexplained hyperlactatemia. At study baseline this 19 year old female had a low serum bicarbonate that was not further evaluated. After receiving 0.5 mg ETV for approximately 3 months she developed fatigue, malaise, and hyperlactatemia. She received symptomatic treatment and ETV was discontinued and her clinical condition improved. However, her symptoms, low serum bicarbonate, and elevated serum lactate recurred and remained intermittently present over the next 6 months while off ETV. No alternative explanation for her condition has been identified but the persistence of symptoms for many months after discontinuation of study drug argues against a direct effect of the ETV. In other nucleoside analogue-related lactic acidosis syndromes, signs and symptoms generally do not persist months after discontinuation of the causative drug.

7.1.4 Other Search Strategies

Additional searches were performed to evaluate some of the toxicities identified in pre-clinical studies as discussed in the previous section. A special search was conducted for neurologic events. This search involved pooling MedDRA Nervous System AEs and selected Psychiatric AEs in an attempt to further evaluate the rates of neurologic AEs and relationship to study drug. Similarly, all events of reported malignancies were pooled across all clinical trials.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the pivotal studies, subjects were evaluated in the clinical site every 4 weeks during the first year of study drug dosing, then every 8 weeks during the second year of dosing. Study subjects entering the off-treatment follow-up were evaluated every 4 weeks. At each visit, study subjects were asked to report any new signs or symptoms or any change in previously reported signs or symptoms. These events were scored according to severity using the modified WHO toxicity table and the relationship between the event and blinded study drug was determined by the local investigator.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant categorized AEs using the MedDRA dictionary of System Organ Class and Preferred Terms. For Study 022, MedDRA version 6.1 was used. For Study 027, MedDRA version 7 was used. Cross-check of investigators' "verbatim" description of AEs compared to the designated MedDRA Preferred Term suggests that the applicant's categorization of AEs was appropriate. There were some instances in which it was difficult to determine the distinctions between AEs termed "ALT increased," "hepatic enzymes increased," "hepatitis," and . It appeared that investigators may have used different "verbatim" terms for the same patient at different visits and these slightly different terms were carried over into the designated MedDRA Preferred Terms. These minor differences in Preferred Terms did not appear to have any impact on the analysis of significant AEs.

7.1.5.3 Incidence of common adverse events

The safety review included data on 1347 nucleoside-naïve subjects (679 ETV subjects, 668 LVD subjects) and 373 LVD-refractory subjects (183 ETV subjects and 190 LVD subjects). The applicant evaluated the rates of all AEs, AEs of Grade 2 to 4 intensity (moderate to life-threatening), AEs of Grade 3 and 4 intensity (severe to life-threatening), AEs identified as possibly, probably, or certainly related to study drug administration, and treatment-related AEs of Grades 2 to 4. These categories of AEs were compared across the treatment groups and for both the on-treatment and off-treatment periods. The rates of AEs reported in different categories were confirmed by the Medical Officers for each of the studies and for the pooled data.

Adverse events were reported frequently in nucleoside-naive subjects although there were few differences in the pattern of AEs reported by ETV-treated subjects compared to LVD-treated subjects. On treatment AEs reported in $\geq$ 5% of subjects 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 subjects 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%). Adverse events were reported in smaller numbers of nucleoside-naive subjects during the off-treatment follow-up period and very few events were observed in $\geq$ 5% of subjects (increased ALT: 3% ETV and 11% LVD, headache: 5% ETV and 6% LVD). During the off-treatment period, only increased ALT occurred more frequently in LVD subjects than ETV subjects. Other AEs occurred in similar numbers of subjects in both groups.

The pattern of commonly reported AEs was very similar in the LVD-refractory subjects. On treatment AEs reported in $\geq$ 5% of subjects 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 subjects receiving LVD (11%) than in those receiving ETV (3%) and fever and sore throat were reported more frequently in ETV subjects (9% and 7%, respectively) than in LVD patients (4% and 2%). Reflective of the relatively small proportion of LVD-refractory subjects who entered off-treatment follow-up, few subjects experienced AEs during the off-treatment period. There were no significant differences in the pattern of off-treatment AEs between the treatment groups.

7.1.5.4 Common adverse event tables

Adverse events were very common in the study populations. For this reason, the applicant chose to present tables containing common AEs occurring in ≥ 3% of subjects in any treatment arm. These events have been compiled and displayed below using a cut-off rate of ≥ 5% for the nucleoside-naïve and LVD-refractory groups.

Table 7.1.5.4A: Adverse Event Reported in ≥ 5% of Subjects in any Treatment Arm for Pooled Nucleoside-Naïve and LVD-Refractory Groups – On Treatment

Adverse Event (MedDRA Preferred Term)	Nucleoside-Naïve		LVD-Refractory	
	ETV (N=679)	LVD (N=668)	ETV (N=183)	LVD (N=190)
All patients with AE	552 (81%)	551 (82%)	156 (85%)	155 (82%)
Abdominal pain	43 (6%)	45 (7%)	8 (4%)	12 (6%)
Abdominal pain upper	69 (10%)	62 (9%)	15 (8%)	24 (13%)
ALT increased	22 (3%)	47 (7%)	6 (3%)	20 (11%)
Arthralgia	53 (8%)	38 (6%)	10 (5%)	12 (6%)
AST increased	9 (1%)	22 (3%)	6 (3%)	9 (5%)
Back pain	49 (7%)	48 (7%)	8 (4%)	11 (6%)
Blood amylase increased	29 (4%)	25 (4%)	4 (2%)	3 (2%)
Cough	73 (11%)	64 (10%)	20 (11%)	17 (9%)
Diarrhea	59 (9%)	45 (7%)	13 (7%)	14 (7%)
Dizziness	42 (6%)	39 (6%)	14 (8%)	11 (6%)
Dyspepsia	48 (7%)	43 (6%)	10 (5%)	7 (4%)
Fatigue	66 (10%)	63 (9%)	26 (14%)	22 (12%)
Headache	137 (20%)	128 (19%)	35 (19%)	34 (18%)
Influenza	55 (8%)	43 (6%)	7 (4%)	10 (5%)
Insomnia	30 (4%)	36 (5%)	10 (5%)	12 (6%)
Myalgia	34 (5%)	31 (5%)	12 (7%)	8 (4%)
Nasopharyngitis	79 (12%)	78 (12%)	16 (9%)	19 (10%)
Nausea	42 (6%)	34 (5%)	13 (7%)	17 (9%)
Pharyngolaryngeal pain	36 (5%)	29 (4%)	13 (7%)	3 (2%)
Pyrexia	56 (8%)	46 (7%)	16 (9%)	7 (4%)
Rhinorrhea	26 (4%)	15 (2%)	4 (2%)	6 (3%)
Upper respiratory tract infection	121 (18%)	108 (16%)	30 (16%)	22 (12%)

Source: Medical Officers' review of the electronic datasets.

The applicant also tabulated the AEs that were considered treatment related and of Grade 2 to 4 severity (moderate to life threatening). These events represent those that are more likely to be related to study drug and require intervention, either another type of treatment or interrupting or discontinuing the study treatment. Events of this severity were relatively uncommon in either nucleoside-naïve or LVD-refractory subjects or across study treatments. This type of tabulation as shown in Table 7.1.5.4B is generally considered appropriate for inclusion in the product label for a new drug.

Table 7.1.5.4B: Selected Adverse Events Reported in Pooled Nucleoside-Naïve and LVD-Refractory Groups: Grades 2-4, Treatment-Related.

Adverse Event (MedDRA Preferred Term)	Nucleoside-Naïve		LVD-Refractory	
	ETV (N=679)	LVD (N=668)	ETV (N=183)	LVD (N=190)
All patients with any Grade 2 to 4 AE	101 (15%)	117 (18%)	44 (24%)	45 (24%)
Abdominal pain	3 (<1%)	3 (<1%)	1 (<1%)	6 (3%)
ALT increased	8 (1%)	30 (4%)	5 (3%)	11 (6%)
Arthralgia	4 (<1%)	4 (<1%)	0	2 (1%)
AST increased	3 (<1%)	14 (2%)	5 (3%)	6 (3%)
Blood amylase increased	15	10 (1%)	2 (1%)	0
Depression	1 (<1%)	4 (<1%)	0	0
Diarrhea	3 (<1%)	0	2 (1%)	0
Dizziness	3 (<1%)	2 (<1%)	0	2 (1%)
Dyspepsia	3 (<1%)	1 (<1%)	2 (1%)	0
Fatigue	8 (1%)	7 (1%)	6 (3%)	5 (3%)
Headache	15 (2%)	14 (2%)	8 (4%)	2 (1%)
Lipase increased	16 (2%)	14 (2%)	5 (3%)	3 (2%)
Nausea	4 (<1%)	2 (<1%)	1 (<1%)	3 (2%)
Pyrexia	1 (<1%)	1 (<1%)	0	1 (<1%)

Source: Medical Officers' review of the electronic datasets.

7.1.5.5 Identifying common and drug-related adverse events

There was no consistent pattern of drug-related adverse events in the ETV pivotal trials when ETV was compared to LVD. None of the Phase 2 or Phase 3 studies of sufficient length to identify AEs were placebo-controlled, so it is possible that drug-related adverse events occurred but were not detected because they occurred at the same rate as seen in the active control LVD groups. There appeared to be an ETV dose-response effect in the occurrence of pooled neurologic AEs in the Phase 2 Study 005 compared to LVD. That dose-response effect was not seen in the other Phase 2 Study 014 and no difference in rates of neurologic AEs was apparent in the larger Phase 3 studies.

In the pooled study populations and in the individual Phase 3 studies, there was a trend toward fewer AEs of increased ALT among ETV subjects compared to LVD subjects. This may be reflective of the fact that fewer ETV subjects experienced ALT flares either during blinded study treatment or in off-treatment follow-up (see Section 7.1.3.3 Other significant adverse events). The differences were not large and not statistically significant but were consistent across the studies.

7.1.5.6 Additional analyses and explorations

The applicant provided additional subgroup analyses for the demographic and disease covariates race, gender, age, region, baseline ALT, and baseline cirrhosis on biopsy. For these analyses, all ETV subjects in the pivotal studies were pooled (nucleoside-naïve + LVD-refractory).

The applicant identified minor differences in clinical AEs based on race. In this analysis, the only subgroups with adequate numbers to evaluate were Asians and Whites. Among ETV-treated subjects, Asians had higher rates of pyrexia (13% compared to 5% in Whites), dizziness (10% compared to 4%), upper respiratory infection (31% compared to 6%), cough (18% compared to 5%), nasopharyngitis (15% compared to 7%), headache (24% compared to 15%), and pooled neurologic AEs (27% compared to 17%). Among ETV-treated subjects, Whites had higher rates of abnormalities in platelets (10% compared to 4% in Asians), PT (49% compared to 20%), INR (41% compared to 15%), alkaline phosphatase (11% compared to 5%), albumin (10% compared to 4%), creatinine (8% compared to 2%), and hypocarbia (31% compared to 21%). The applicant notes that similar clinical and laboratory differences across racial groups were also observed in subjects receiving LVD. There were no identifiable differences between the racial groups in terms of SAEs or ALT flares.

Minor differences in clinical AEs and laboratory abnormalities were also identified based on gender. Most of the differences between genders such as abnormalities in hemoglobin levels and hematuria are also noted in the general population. Female subjects receiving ETV had a higher rate of reported nausea (11% vs 5%). No differences were noted in the rates of SAEs or ALT flares. Female subjects receiving ETV had higher rates of hemoglobin abnormalities compared to male subjects (11% vs <1%) and higher rates of hematuria (72% vs 38%). Male subjects receiving ETV reported higher rates of abnormalities in total bilirubin (35% vs 22%), lipase (30% vs 14%), and hyperglycemia (22% vs 10%). Similar gender differences were observed in both the ETV-treated and the LVD-treated subjects.

Differences in clinical AEs and laboratory abnormalities based on age were consistent with the expected longer duration of illness in older subjects and changes related to aging. Subjects 16 to 20 years of age made up 6% of the pivotal study population; subjects $\geq$ 65 years of age made up 4% of the pivotal study population. In spite of small numbers, it appeared that subjects $\geq$ 65 years of age had a higher rate of clinical AEs, SAEs, neoplasms, and some laboratory abnormalities (WBC, platelets, PT, INR, alkaline phosphatase, albumin, BUN, hyperglycemia, and hypernatremia). Subjects 16-20 years of age had higher rates of acne, upper abdominal pain, asthenia, somnolence, and elevated lipase compared to subjects 21-64 years of age. Similar differences were observed in both ETV and LVD treated groups.

There did not appear to be significant differences in potential drug toxicity based on subjects' baseline ALT using a cut-off value of < 2.6 x ULN or ≥ 2.6 x ULN. Subjects with baseline liver biopsy indicative of cirrhosis had similar rates of ALT flares and hepatic SAEs compared to subjects without cirrhosis. Subjects with cirrhosis had higher rates of abnormalities of WBC, platelets, PT, INR, alkaline phosphatase, hyperglycemia, and ALT > 2 x baseline. The applicant states that these differences were generally consistent across ETV and LVD-treated groups and were consistent with the stage of underlying disease. Increases in amylase and lipase were observed more often in LVD-treated subjects with cirrhosis than in ETV-treated subjects.

7.1.6 Less Common Adverse Events

Less common AEs (< 1%) were identified in the safety database but the number of subjects in the database was not adequate to conduct a formal analysis across treatment groups for events occurring at low frequency. The occurrence of malignancies which might qualify as less common events was evaluated in detail throughout the clinical development program and is reported in Section 7.1.11 Human Carcinogenicity.

7.1.7 Laboratory Findings

Evaluation of clinical laboratory parameters was conducted by analyzing the proportion of subjects in each treatment group who experienced marked laboratory abnormalities during the study. Marked laboratory abnormalities were identified using a standardized table of Recommendations for Grading Acute and Subacute Adverse Events included in the study protocol (modified from WHO recommendations). The applicant evaluated laboratory abnormalities during both on-treatment and off-treatment periods; this integrated safety review is focused on findings occurring while patients were receiving study drug. In addition to evaluating marked laboratory abnormalities, the Medical Officer also assessed mean changes from baseline for selected laboratory tests.

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory monitoring for safety included assessments of routine hematology and coagulation studies, serum biochemical studies, and urinalysis at screening, baseline, and each study visit.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory datasets were available for all Phase 2 and 3 studies submitted as part of the ETV NDA. Laboratory data reviewed for this Clinical Review focused on that from the pivotal studies (Studies 022, 027, 026, and the 1 mg ETV and LVD arms of Study 014). In all of these studies, the rates of laboratory abnormalities in ETV-treated subjects could be compared to those

in LVD-treated subjects. For this integrated safety summary, nucleoside-naïve subjects were pooled and LVD-refractory subjects were pooled.

7.1.7.3 Standard analyses and explorations of laboratory data

Clinical laboratory monitoring for safety included assessments of routine hematology and coagulation studies, serum biochemical studies, and urinalysis at screening, baseline, and each study visit. Almost all patients who received blinded study drug had laboratory data available for review. Over 90% of study subjects had laboratory data at baseline and at the Week 48 visit. There were slightly more missing values for laboratory tests such as PT and INR compared to routine serum chemistry studies and hematology studies. Similarly, lipase levels were not routinely monitored at all study sites.

7.1.7.3.1 Analyses focused on measures of central tendency

The applicant did not provide an analysis of mean or median changes from baseline in laboratory values. The Medical Officers conducted this type of analysis for selected laboratory parameters, primarily those related to liver function. For most of the laboratory parameters evaluated, there were insignificant changes over the first 48 weeks of study drug dosing. Abnormal ALT consistent with active HBV was one of the entry criteria for the Phase 3 studies. As might be expected for a drug with activity against HBV, serum ALT decreased from baseline to Week 48 in all groups receiving ETV in the 3 studies. Subjects receiving LVD in the 2 nucleoside-naïve studies experienced a similar decrease in mean ALT from baseline to Week 48 but not those in the LVD-refractory study.

Table 7.1.7.3.1A: Change from Baseline for Selected Laboratory Tests in Entecavir Phase 3 Studies

	Study 022		Study 027		Study 026	
Mean Laboratory Parameter	ETV 0.5 mg (N=354)	LVD 100 mg (N=355)	ETV 0.5 mg (N=325)	LVD 100 mg (N=313)	ETV 1 mg (N=143)	LVD 100 mg (N=142)
ALT (IU)	N=333*	N=318	N=310	N=297	N=134	N=127
Baseline	141	147	141	141	121	133
Week 48	36	45	32	41	43	121
Change	-105	-102	-109	-101	-82	-13
Creatinine (mg/dL)	N=334	N=315	N=307	N=295	ND	ND
Baseline	0.95	0.92	0.91	0.93		
Week 48	0.96	0.95	0.92	0.93		
Change	0.004	0.03	0.01	-		
INR	N=300	N=289	N=255	N=256	N=113	N=105
Baseline	1.08	1.08	1.12	1.10	1.07	1.08
Week 48	1.04	1.04	1.06	1.06	1.03	1.08
Change	-0.04	-0.04	-0.06	-0.04	-0.04	-
Total bilirubin (mg/dL)	N=335	N=315	N=310	N=296	N=131	N=126
Baseline	0.87	0.80	0.86	0.79	3.7	3.8

Week 48	0.83	0.81	0.84	0.75	3.6	3.8
Change	-0.04	0.01	-0.01	-0.04	-0.2	-0.1

Source: Medical Officers' review of the electronic datasets.
*N for each parameter = number of subjects with paired baseline and Week 48 values.
ND = Not done

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The primary laboratory safety analysis presented by the applicant evaluated the proportion of subjects in each treatment group who developed markedly abnormal values in the Phase 3 studies. As noted above, the applicant utilized a laboratory toxicity grading system modified from WHO guidelines. This toxicity grading system was considered acceptable for use in clinical trials. Laboratory abnormalities were evaluated in terms of occurrence of any toxicity grade (Grades 1 to 4) or occurrence of marked abnormalities (Grades 3 or 4). Laboratory abnormalities that were considered clinically significant by the investigator were also reported as AEs and have been included in the discussion of those events in Section 7.1.5.4 Common adverse events.

The most commonly observed hematologic or 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 only 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 also 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 cohorts. 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. In general, mean ALT and AST levels decreased among nucleoside-naïve subjects on treatment in both treatment arms as noted above but significant numbers of subjects experienced Grade 3 or 4 ALT elevations after the baseline value: 21% of ETV subjects and 25% of LVD subjects. Among LVD-refractory subjects, Grade 3 or 4 ALT elevations were also reported in a significant number of subjects and were more common in the LVD group: 19% of ETV subjects and 31% of LVD subjects.

A representative sample of Grade 3 or 4 laboratory abnormalities is displayed in Table 7.1.7.3.2A. For many laboratory tests, no or very few subjects in the Phase 3 studies experienced a laboratory abnormality ≥ Grade 3. For example, there were no subjects in any of the pivotal

studies with Grade 3 or 4 abnormalities of creatinine while receiving blinded study drug and very few with Grade 3 or 4 hematologic parameters.

Table 7.1.7.3.2A: Subjects Experiencing ≥ Grade 3 Selected Laboratory Abnormalities in Entecavir Pivotal Studies: On-Treatment

	Nucleoside-Naïve		LVD-Refractory	
Laboratory Parameter	ETV 0.5 mg (N=679)	LVD 100 mg (N=668)	ETV 1 mg (N=183)	LVD 100 mg (N=190)
Absolute neutrophil count	2 (<1%)	1 (<1%)	4 (2%)	1 (<1%)
ALT	140 (21%)	170 (25%)	35 (19%)	59 (31%)
Amylase	17 (3%)	14 (2%)	7 (4%)	7 (4%)
AST	48 (7%)	64 (10%)	12 (7%)	37 (19%)
Bicarbonate – low	4 (<1%)	4 (<1%)	1 (<1%)	4 (2%)
Glucose – high	23 (3%)	19 (3%)	4 (2%)	5 (2%)
Glucose – low	3 (<1%)	3 (<1%)	0	0
Hemoglobin	1 (<1%)	0	0	0
INR	7 (1%)	5 (<1%)	3 (2%)	7 (4%)
Lipase	33 (5%)	28 (4%)	11 (6%)	10 (5%)
Platelets	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Potassium – high	5 (<1%)	5 (<1%)	2 (1%)	0
PT	9 (1%)	3 (<1%)	4 (2%)	7 (4%)
Total bilirubin	13 (2%)	13 (2%)	5 (3%)	3 (2%)
Urine, blood	66 (10%)	75 (11%)	17 (9%)	18 (9%)
Urine, glucose	33 (5%)	26 (4%)	8 (4%)	13 (7%)
Urine, protein	8 (1%)	10 (1%)	5 (3%)	4 (2%)

Source: Medical Officer's review of the clinical datasets.

Another way of evaluating this type of laboratory information is to search for significant shifts from baseline. The applicant tabulated the number and proportion of subjects who experienced a worsening of a laboratory value from baseline to a Grade 3 or 4 toxicity level. This method essentially "corrects" for those subjects who had markedly abnormal values at study entry and then improved over time. It does not account for subjects who may have improved and then worsened again (eg., a subject who started at Grade 3 ALT, improved to Grade 1 toxicity level, the worsened to Grade 3 later). A representative sample of laboratory values displayed in this way is shown in Table 7.1.7.3.2B and will likely be displayed in the product label.

Table 7.1.7.3.2: Subjects Increasing from Baseline to Grade 3 or Grade 4 Toxicity in Entecavir Pivotal Trials: On Treatment

	Nucleoside-Naïve		LVD-Refractory	
Laboratory Parameter	ETV 0.5 mg	LVD 100 mg	ETV 1 mg	LVD 100 mg

	(N=679)	(N=668)	(N=183)	(N=190)
ALT	77 (11%)	105 (16%)	22 (12%)	46 (24%)
Amylase	16 (2%)	13 (2%)	5 (3%)	5 (3%)
AST	35 (5%)	50 (7%)	10 (5%)	32 (17%)
Glucose – high	9/513 (2%)	7/487 (1%)	3/169 (2%)	2/167 (1%)
INR	6/621 (<1%)	4/598 (<1%)	3/169 (2%)	7/172 (4%)
Lipase	32/429 (7%)	28/417 (7%)	8/174 (5%)	8/141 (6%)
Total bilirubin	13 (2%)	11 (2%)	5 (3%)	3 (2%)
Hematuria	60 (9%)	66 (10%)	16 (9%)	12 (6%)
Glycosuria	24 (4%)	19 (3%)	8 (4%)	12 (6%)

Source: Adapted from AI463022: Clinical Study Report Addendum 01, Supplemental Tables, AI463027: Clinical Study Report Addendum 01, Supplemental Tables, AI463026: Clinical Study Report, Supplemental Tables, and AI463014 Clinical Study Report, Supplemental Tables.
Note: Not all subjects had all laboratory tests. In cases where the number of subjects with the test was substantially different from the number of subjects treated, the proportions are calculated based on number of subjects with the test and these numbers are shown in the table (eg., 9/513 subjects had fasting glucose available for determining the proportion with elevated glucose).

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Individual study subjects who developed laboratory abnormalities that were considered clinically significant were reported as AEs. Subjects who discontinued study drug because of marked laboratory abnormalities were included in the discussion of AEs resulting in study drug discontinuation presented in Section 7.1.3.2.

7.1.7.4 Additional analyses and explorations

The applicant also evaluated selected laboratory parameters in slightly different ways. Most subjects in the study populations had abnormal laboratory parameters at baseline, particularly among the liver-related laboratory tests. In this setting, it is useful to evaluate the changes in laboratory values over the course of study drug dosing in order to evaluate potential drug-related increases in abnormalities.

The applicant evaluated the changes from baseline in liver-related laboratory tests in several different ways. The most clinically important of these was the evaluation of ALT flares defined as occurrence of an ALT > 2 x the baseline value and 10 x ULN (as discussed in Section 7.1.3.3 Other significant adverse events).

The toxicity guidelines for creatinine elevation set the cut-off for Grade 3 at a creatinine > 3 x ULN. In clinical practice, creatinine increases less than this cut-off would prompt an evaluation. A more sensitive method of evaluating smaller but significant changes in creatinine is to calculate the proportion of subjects experiencing $\geq$ 0.5 mg/dL change in creatinine from baseline over time. In this analysis, the applicant identified 7 ETV subjects and 9 LVD subjects with a >

0.5 mg/dL increase in creatinine over baseline in the nucleoside-naïve population. Among LVD-refractory subjects, 3 ETV and 2 LVD subjects experienced this level of increase in creatinine.

7.1.7.5 Special assessments

Assessment of hepatotoxicity, considered a special laboratory assessment for reviews of other drugs is an integral part of both the efficacy and safety evaluation of any drug for chronic HBV. For an evaluation of potential hepatotoxicity, refer to the discussion of ALT flares presented in Section 7.1.3.3 Other significant adverse events.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Measurement of vital signs was performed for subjects in all the pivotal studies at screening, baseline, and at every study visit. These measurements included blood pressure, heart rate, respiratory rate, and temperature.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Blood pressure, heart rate, respiratory rate, and temperature were evaluated for each study across treatment groups. No pooled analyses were performed.

7.1.8.3 Standard analyses and explorations of vital signs data

The assessment of vital signs identified no clinically relevant differences between the treatment groups. Results of the assessments raised no safety concerns.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were conducted by either the applicant or the Medical Officers.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Evaluation of the effect of ETV on ECG parameters began with a series of pre-clinical assessments. There was no evidence that ETV had a significant effect on QT prolongation from the *in vitro* rabbit Purkinje fiber assay or potassium channel currents (hERG) assay and no evidence of an effect *in vivo* in animal toxicology studies in dogs and monkeys. Also, ETV is

known not to interact with the CYP450 enzymes and so is unlikely to interact with drugs known to have arrhymogenic effects that are metabolized by that system.

The effects of ETV on subjects in the clinical trials program was evaluated in a retrospective analysis of subjects from 5 of the Phase 1 studies in which ECGs could be paired with ETV concentrations (Studies 001, 002, 010, 033, and 034). This analysis included subjects receiving the to-be-marketed doses of 0.5 and 1 mg and also doses up to 40 mg. No significant effect on QTc was identified in this analysis. For additional description of the retrospective ECG review, refer to Section 5.3 Exposure-Response Relationships of this review and the Clinical Pharmacology Review by Dr. Bergman. Based on the results of the pre-clinical studies and the review of ECG data from the selected Phase 1 studies, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Based on the results of the pre-clinical studies and the review of ECG data from the selected Phase 1 studies, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.3 Standard analyses and explorations of ECG data

Based on the results of the pre-clinical studies and the review of ECG data from the selected Phase 1 studies, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.4 Additional analyses and explorations

Based on the results of the pre-clinical studies and the review of ECG data from the selected Phase 1 studies, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.10 Immunogenicity

As a therapeutic nucleoside analogue, ETV is not expected to illicit an immune response. The applicant provided some pre-clinical animal study data suggesting that ETV may have some macrophage chemotactic properties in mice but these properties were not observed with human mononuclear cells *in vitro*.

7.1.11 Human Carcinogenicity

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 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. This promising data from the animal model was influential in the development program.

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. As might be expected in this population, the most commonly reported malignancy was HCC, occurring in 7 ETV and 4 LVD subjects. Other malignancies occurring in more than one subject included: gastric carcinoma, basal cell carcinoma, prostate cancer, and breast cancer.

The Medical Officers reviewed all narrative summaries and CRFs 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 rates 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 a description of the cancer surveillance studies in HBV-infected patients see Section 7.1.12 Special Safety Studies). 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.

7.1.12 Special Safety Studies

BMS commissioned 2 retrospective studies to elicit cancer rate data from 2 large populations of patients at risk for HBV-related cancer. The goal of these studies was to provide background information in populations with chronic HBV to assist in the assessment of cancer rates in patients receiving ETV.

The first study (called the US Study) was conducted using the automated patient data records and medical records of patients enrolled in the Kaiser Permanente Medical Care Program of Northern California (KPMCP) and the Henry Ford Health System (HFHS) based in Detroit, MI. The 2 medical systems provide medical care to over — patients in the coverage areas in HFHS and — in KPMCP). Both systems maintain tumor registries that feed into the NCI Surveillance Epidemiology and End Results Program. Electronic databases were searched to identify the population ≥ 16 years of age that was in the database between January 1, 1995, and December 31, 2001. Three non-overlapping cohorts were defined based on a level of confidence of a diagnosis of chronic HBV: confirmed chronic HBV (using an algorithm of 2 HBV antigen or DNA tests 6 months apart or other confirmed chronic HBV diagnosis), HBsAg+ cohort (one positive test, not confirmed by other methods), and ICD-9 cohort (patients diagnosed with HBV at any time but who did not have a documented HBsAg+ test). The comparison cohorts for each of the 3 HBV cohorts included 50 comparison patients for each HBV patient, matched for health system, age +/- 5 years, and sex and who had no indicators of HBV infection.

The second study (called the Taiwan Study) used data derived from an ongoing community based cancer screening program conducted from 1991 with follow-up through 2003. Seven townships in Taiwan were selected to represent all the Taiwanese islands and both urban and rural areas. 23,943 residents out of the population's registered 89,293 persons (26.8%) gave informed consent and enrolled in the study. Patients were interviewed by public health nurses, and male subjects were tested at the time of enrollment for HBsAg, HBeAg, and anti-HCV antibodies. Female subjects were tested only for HBsAg. Study subjects who were HBsAg positive, HCV positive, had abnormal ALT, AST or AFP, or had a history of cirrhosis or HCC had abdominal ultrasound. HBsAg positive subjects had repeat ultrasound every 6 to 12 months and those with cirrhosis had repeat ultrasounds every 3 to months during the follow-up period. Subjects were divided into Test and Control groups according to baseline HBsAg status.

Follow-up data was linked with data from the National Cancer Registry and from death certificates.

These studies identified rates of cancer overall and for specific tumor types in the HBV group compared to the general population in the U.S. and Taiwanese cohorts. These studies confirmed that HCC occurs much more commonly in people with chronic HBV than in the general population. The U.S. study identified a rate of HCC of 4.6 per 1000 person-years among patients with chronic HBV compared to 0.02 per 1000 person-years in the comparison cohort. The U.S. study suggested that patients with presumed chronic HBV according to the study algorithm were at higher risk for developing any cancer (all sites or excluding liver) and more likely to develop non-Hodgkins lymphoma. In the Taiwan study, patients identified as having HBV had a rate of liver cancer of 3.6 per 1000 person-years compared to the rate of 0.4 per person-years in the non-HBV cohort. In this population, patients with HBV infection were also more likely to develop cancer of any type than uninfected controls and more likely to develop pancreatic cancer.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Based on clinical experience with other therapeutic nucleoside analogues and the mechanism of action of ETV, it is not expected that ETV will be associated with any abuse potential or withdrawal phenomena. The occurrence of ALT flares after discontinuation of ETV (or other anti-HBV drugs) represents recurrence of uncontrolled HBV viremia and not a true withdrawal syndrome.

7.1.14 Human Reproduction and Pregnancy Data

There is no controlled study data in pregnant women receiving ETV. Women enrolled in the clinical trials who became pregnant while on study drug were required to discontinue drug.

There were 8 pregnancies reported in women enrolled in the ETV development program, 4 received ETV and 4 received LVD and all were in Study 022. Among these women, 2 reported spontaneous abortions and 2 reported induced abortions. One woman was lost to follow-up before delivery. Three women delivered living infants, 2 of them reported to be healthy.

Subject #022-27-10645 had a complex prenatal history and was reported to have delivered a premature infant with a significant brain abnormality. She began blinded study drug (ETV) on July 5, 2002. She discontinued drug on —, and pregnancy was confirmed — The subject reported what was thought to be a spontaneous abortion on — and fetal ultrasound in the ER was consistent with fetal demise. She was discharged from the ER with doxycycline and methylergonovine. After a protocol exception was obtained, the subject restarted blinded study drug on — Follow-up ultrasound on — revealed an intact pregnancy and viable fetus and study drug was permanently discontinued. The subject was noted to have persistent vaginal bleeding throughout the pregnancy. She delivered a premature, male infant (33 weeks gestation) who was noted to have "a problem with the cerebral cortex." No other details of the infant's condition were available and the family refused to release further information.

7.1.15 Assessment of Effect on Growth

To date, all of the clinical trials of ETV have been conducted in adults. Therefore, no formal assessment of the effect of ETV on growth has been performed. Evaluation of ETV in children has not been initiated at this time.

7.1.16 Overdose Experience

There is no experience with overdose of ETV. Phase 1 studies evaluated 14 days of dosing of ETV at doses up to 20 mg daily and single doses up to 40 mg without significant problems.

7.1.17 Postmarketing Experience

At this time, ETV has not been approved for use by any national regulatory authority so there is no post-marketing experience with the drug.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Please refer to Table 4.2A for a description of the ETV clinical trials submitted for this safety review. In addition, the number of subjects enrolled in the clinical pharmacology studies is summarized in Table 7.2.1.1A. For a review of the safety evaluations conducted during the Phase 1 studies, refer to the Clinical Pharmacology Review by Dr. Bergman.

Table 7.2.1.1A: Subjects Enrolled in Entecavir Clinical Pharmacology Studies

Population	ETV Only[a]	ETV+Other[b]	Any ETV[c]	Placebo or Other[d]	Total Number
Healthy subjects	493	117	494	165	535
Non-healthy subjects[e]	44	0	44	0	44
All subjects	537	117	538	165	579

Source: NDA 21-797, Clinical Safety Summary, Volume 7, Table 7, page 129.
Note: A subject may be counted in more than 1 treatment category if study design included multiple treatment periods in which ETV was administered alone in 1 period, placebo in another, and/or ETV with a concomitant study medication in another period.
[a]ETV Only: subjects received ETV as the sole study drug for $\geq$ 1 day.
[b]ETV+Other: subjects received ETV + another protocol specified study drug for > 1 day.

[c]Any ETV: subjects receieved ETV with or without other study drug
[d]Placebo/Other: subjects received either only placebo, or only a sportocol-specified study drug other than ETV for > 1 day without ETV during that period.
[e]Includes 28 subjects with renal impairment and 16 subjects with hepatic impairment.

7.2.1.2 Demographics

The following table provides demographic data for all subjects included in the applicant's safety database which includes Studies 004, 005, 007, 012, 014, 015, 022, 026, 027, and 056.

Table 7.2.1.2A: Demographic Characteristics of Subjects in Safety Cohort

Demographic Characteristic	ETV	LVD	Placebo	Total
Received study drug	1392	899	108*	2399
Male/Female (%)	76%/24%	75%/25%	77%/23%	76%/24%
Mean age in years (range)	38.2 (16-76)	39.3 (16-80)	32 (18-73)	38.4 (16-80)
Race				
Asian	780 (56%)	418 (46%)	106 (98%)	1304 (54%)
Black/African American	27 (2%)	15 (2%)	0	42 (2%)
Hispanic/Latino	6 (<1%)	1 (<1%)	0	7 (<1%)
Native Hawaiian/Pacific Islander	1 (<1%)	4 (<1%)	0	5 (<1%)
Other	16 (1%)	6 (<1%)	0	22 (<1%)
White	562 (40%)	455 (51%)	2 (2%)	1019 (42%)
Geographic region				
Asia	661 (47%)	331 (37%)	101 (94%)	1093 (46%)
Europe	446 (32%)	346 (38%)	3 (3%)	795 (33%)
North America	183 (13%)	130 (14%)	4 (4%)	317 (13%)
South America	102 (7%)	92 (10%)	0	194 (8%)

Source: Medical Officers' review of the electronic datasets.
Note: In some studies Pacific Islanders were grouped demographically with Asians and in others with Native Hawaiian. Since Asians were a large subgroup, this table combines "Asian" and "Asian/Pacific Islander" designations together.
*Communication from the applicant notes that 105 of 108 subjects receiving placebo subsequently received ETV for some period of time.

7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3A 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 7.2.1.3A: 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	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	68.2	51.1

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

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The primary sources of data for the safety review were the pivotal trials, Studies 022, 027, 026, and the 1 mg ETV and 100 mg LVD arms from Study 014. Other studies reviewed for safety included the remaining dose levels of Study 014 (see individual study review in Section 10.1 Appendix), Study 015 the pilot study in liver transplant recipients, and Study 038 the study in HIV/HBV co-infected subjects. Data from Studies 015 and 038 were not considered of inferior quality but were pertinent to special populations and not generalizable to efficacy and safety in the broader population. Results from Studies 015 and 038 are discussed briefly in Sections 6.1.4 Efficacy Findings and 8.3 Special Populations and are more fully described in Section 10.1 Review of Individual Study Reports.

7.2.2.2 Postmarketing experience

As noted above, there is no post-marketing experience with ETV since it has not been approved for use in any country.

7.2.2.3 Literature

The applicant included an extensive review of the literature related to treatment of chronic HBV, pre-clinical reports from the ETV development program, and correlation of different endpoints. This information was informative but not critical to the NDA review of efficacy or safety.

7.2.3 Adequacy of Overall Clinical Experience

It is the opinion of the Medical Officers that the overall clinical experience with ETV presented in this NDA is adequate to assess the safety of the drug. Longer follow-up will be needed as clinical guidelines for duration of treatment may exceed the duration of initial drug testing. Subjects enrolled in the studies reported in the NDA continue to be followed either in the pivotal studies or in rollover or long-term observational studies conducted by the applicant.

In general, an adequate number of subjects were enrolled in the pivotal studies and exposed to study drug to assess the safety of ETV compared to LVD. As noted previously, there were not adequate numbers of blacks/African Americans enrolled in the clinical trials to be assured that the safety profile in this subgroup is similar to those of other racial groups. The doses and duration of exposure in nucleoside-naïve and LVD-refractory subjects were reasonable and adequate to support initial review of safety. The safety of longer-term dosing will be evaluated in future submissions as subjects continue dosing through the second year of the Phase 3 studies and rollover into other protocols. The design of the pivotal studies utilizing LVD as an active control was appropriate to answer the most important questions regarding comparative safety and efficacy. The potential toxicities identified in pre-clinical testing such as neurologic events and malignancies were evaluated throughout the Phase 2 and 3 drug development program and evaluation is ongoing. The potential class effect of nucleoside analogues, lactic acidosis, was not evaluated prospectively but was evaluated using a search of the pivotal trial safety database. Similarly, the anticipated occurrence of ALT flares, a complication of any active treatment of chronic HBV was evaluated throughout the pivotal studies. The pivotal studies were limited to subjects with compensated liver disease. It is possible that subjects with decompensated liver function may have a different safety profile and an ongoing study is evaluating this issue.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The applicant conducted a number of special animal and *in vitro* tests to determine the possible mechanisms of carcinogenicity for ETV. For detailed review of these studies, refer to the Pharmacology/Toxicology Review by Dr. Pritam Verma. It was concluded that the studies were supportive of the applicant's hypothesis that the pulmonary tumors seen in mice might be a species-specific phenomenon.

7.2.5 Adequacy of Routine Clinical Testing

It is the opinion of the Medical Officers that the routine clinical and laboratory testing conducted during the pivotal and supportive studies was adequate to assess safety. The number, variety, and timing of clinical and laboratory tests were appropriate for the study populations and the disease being studied.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pre-clinical and clinical evaluations of metabolic, clearance, and potential drug interactions were adequate for the class of drug and indication being studied. For a more detailed evaluation

of these issues, refer to the Clinical Pharmacology/Biopharmaceutics Review by Dr. Kim Bergman and the summary of these findings included in Section 5 Clinical Pharmacology.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

In general, the applicant's efforts to evaluate potential AEs that might arise with any new drug were adequate. Although the applicant did not conduct a formal evaluation of ETV's effects on QT interval, there were no signals arising from the pre-clinical studies to suggest that this was an area of concern. They conducted a retrospective analysis of Phase 1 and 2 studies that included ECG and PK data and identified no significant abnormalities in QTc. This approach was discussed at the time of the pre-NDA meeting and was considered acceptable at the time by the Review Team. The evaluation of potential hepatotoxicity was an integral part of the ETV drug development program since in the chronic HBV study populations changes in liver enzymes were used to evaluate both efficacy and safety.

Similarly, the applicant's efforts to evaluate AEs that might be expected with the use of nucleoside analogues (lactic acidosis) or any drug used in the treatment of chronic HBV (ALT flares) were adequate. Pre-clinical testing indicated that ETV has low affinity for human mitochondrial DNA γ polymerase and, therefore, was unlikely to produce significant toxicity related to this mechanism. The applicant's evaluation of ALT flares was consistent with the approach suggested by the Review Team during the drug development program. This analysis concluded that ETV-treated subjects experienced fewer ALT flares than LVD-treated subjects during study dosing and after dosing was discontinued. Evaluations of these toxicities with longer-term dosing are on-going.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of the data available for conducting the safety review was adequate. The proportions of study subjects who had missing data were relatively small and considered acceptable. This was particularly important in regard to obtaining liver biopsies from subjects in the Phase 3 studies. Follow-up of subjects enrolled in the pivotal studies was also acceptable with very few subjects discontinuing study for unknown reasons.

7.2.9 Additional Submissions, Including Safety Update

Important safety data was submitted at the time of the NDA Safety Update, in mid-review. The Safety Update contained extensively updated safety datasets for Study 027 and a revised clinical study report (called Addendum 01) including assessment of off-treatment follow-up. The new data in this submission was incorporated into the primary safety review for Study 027. The Safety Update also included the final study report for Study 038 (HIV/HBV co-infected subjects) and interim data and study reports for Studies 048 (subjects with decompensated liver disease) and 901 (rollover protocol providing open-label ETV+LVD). Data from studies 048 and 901 were considered preliminary and were not formally reviewed for this Clinical Review. Brief

review of these interim study reports did not suggest any new safety concerns although, as expected, subjects with decompensated liver function have frequent AEs and SAEs.

In response to a request for analysis of QTc and PR in additional study populations, the sponsor submitted a re-analysis of ECG parameters using a broader sampling of patients receiving ETV in the Phase 1 and 2 clinical trials. This new information was submitted 2 weeks before the NDA Action Date and was not reviewed in detail prior to the approval. The information was not considered necessary for inclusion in this review or approval of ETV and will be reviewed in full after the approval.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As noted previously, the safety profile of ETV was similar to that of LVD in each of the 4 pivotal studies and in pooled nucleoside-naïve subjects and LVD-refractory subjects. AEs were reported frequently in the nucleoside-naive patients (about 81% in both arms) but there were few differences in the pattern of AEs reported by ETV-treated patients compared to LVD-treated patients. The pattern of commonly reported AEs was very similar in the LVD-refractory patients, with 85% of ETV subjects and 82% of LVD subjects reporting some AE.

If all AEs of any intensity are considered, the most commonly reported events in ETV-treated subjects included: headache, upper respiratory infection, nasopharyngitis ("common cold"), fatigue, cough, abdominal pain, and arthralgia (see Table 7.1.5.4A). Many of these events are common in the general population and in the population of patients with chronic HBV. Because the pivotal studies all used LVD as the active control, it is somewhat difficult to determine true rates of ETV-related AEs. Just because the AE profile for ETV is similar to that of LVD does not mean that the AEs occurring in both treatment groups are not drug-related. Relatively few AEs of moderate to severe intensity were considered drug-related in either treatment group (see Table 7.1.5.4B). Among those most commonly considered drug-related were: headache, fatigue, nausea, abdominal pain, and clinically significant abnormalities of ALT, AST, amylase, and lipase. These events will continue to be monitored in the ongoing Phase 3 clinical trials over longer dosing intervals.

Three categories of events deserve increased attention because of either the potential seriousness of the events or signals from animal toxicology studies. To date, none of these events has been shown to occur more frequently among ETV-treated subjects.

7.3.1 Acute Exacerbations of Hepatitis (ALT Flares)

ALT flares have been described during treatment with all of the approved drugs for chronic HBV and after discontinuation of drugs that have activity against HBV. During the ETV development program, these events were tracked both during treatment and off-treatment follow-up using a standardized definition, the occurrence of ALT values at least 2 x the subject's baseline value and 10 x the ULN. The analysis of ALT flares is discussed in more detail in Section 7.1.3.3 Other significant adverse events.

ALT flares were documented infrequently in nucleoside-naïve patients during the on-treatment period but occurred more often in subjects receiving LVD; 2% ETV-treated subjects and 4% LVD-treated subjects experienced a flare. Flares occurring during the first 12 weeks on study were often accompanied by decreases in HBV DNA and did not necessitate discontinuing study drug but those occurring later in treatment were often accompanied by increases in HBV DNA and more often prompted study drug discontinuation. In Studies 022 and 027 the study designs allowed subjects who met a protocol-defined Response criteria to discontinue treatment and be followed off therapy. Compared to on-treatment, ALT flares occurred slightly more frequently in the off-treatment follow-up period in both treatment groups but were again documented more often among LVD subjects; 4% ETV subjects compared to 8% LVD subjects experienced off-treatment 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, 2% ETV subjects and 10% LVD subjects experienced ALT flares while receiving study drug and 6 LVD patients discontinued study drug because of ALT flares. A much smaller proportion of LVD-refractory subjects in Study 026 met the protocol-defined Response criteria, discontinued their therapy, and were followed off-treatment. During the off-treatment follow-up, 5% ETV subjects and no LVD subjects with follow-up data experienced ALT flares. However, the number of LVD-refractory subjects followed off-treatment is too small to make definitive conclusions regarding rates of ALT flares in this setting.

7.3.2 Nervous System/Neurologic Adverse Events

Because nervous system toxicity was identified in one of the animal toxicology studies and rates of neurologic AEs appeared to be dose-related in one of the Phase 2 studies, neurologic AEs were reviewed in detail for this review (refer to Section 7.1.3.3 Other significant adverse events). Neurologic AEs were evaluated in each of the pivotal studies and for the pooled nucleoside-naïve subjects and pooled LVD-refractory subjects. Rates of all neurologic events were similar across treatment groups in both naïve and LVD-refractory subjects. The proportion of subjects reporting any neurologic event was between 32% and 36%. There were no significant differences in the proportions of subjects reporting anxiety, dizziness, headache, insomnia, migraine, paresthesia, somnolence or syncope across treatment groups. If only subjects reporting Grade 2 to 4 (moderate to severe) neurologic events were tabulated, a slightly higher proportion of LVD-refractory subjects receiving 1 mg ETV were identified compared to LVD. This difference was accounted for by patients reporting a variety of Grade 2, moderate events. No significant pattern of ETV-related neurologic AEs could be identified. These events will continue to be evaluated in the ongoing Phase 3 studies and other clinical trials assessing long-term dosing of ETV.

7.3.3 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 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 of chronic HBVsuggested that administration of ETV to HBV-infected woodchucks decreased the occurrence of HCC in animals that were maintained on the drug long-term. For a more complete discussion of the occurrence of malignancy in the ETV development program, see Section 7.1.11 Human Carcinogenicity.

A review of all cases of malignancy reported up through the most recent IND Safety Update containing data through August 17, 2004, brings the total number of subjects with identified malignancies in the ETV development program to 37. Of these subjects 28 were in the randomized clinical trials populations: 19/1497 ETV subjects (1.3%) and 9/899 LVD subjects (1%). Nine subjects were in special study populations (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. As might be expected in this population, the most commonly reported malignancy was HCC, occurring in 7 ETV, 4 LVD, and 2 ADV subjects. Other malignancies occurring in more than one subject included: gastric carcinoma, basal cell carcinoma, prostate cancer, and breast cancer.

The Medical Officers reviewed all narrative summaries and CRFs of subjects with reported malignancies in the study reports submitted in the NDA. The conclusion was that none of the case descriptions were unusual or reported the occurrence of rare tumor types. There did not appear to be a stereotypical pattern for subjects developing malignancies. 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 subject received study drug for over a year but even this is a relatively short reporting period for assessing carcinogenic potential.

The applicant calculated the rates 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. 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 are comparable to background rates of cancer identified for populations with identified HBV infection in 2 surveillance studies in U.S. and Taiwanese cohort studies (for a description of the cancer surveillance studies in HBV-infected patients see Section 7.1.12 Special Safety Studies).

The applicant continues to track malignancies in all of the ongoing clinical trials of ETV. In addition, BMS has proposed conducting a large, simple, post-marketing safety study to further assess the longer-term risk of cancer in a broad population of patients using ETV. This post-marketing study will be part of a comprehensive pharmacovigilance plan for ETV. For a more detailed description of the proposed post-marketing safety study, refer to Section 8.7 Post-Marketing Risk Management Plan.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

As noted in previous sections, the safety analyses for ETV consisted of review of clinical AEs and laboratory abnormalities in the individual pivotal studies (see Section 10.1 Review of Individual Study Reports) and review of the clinical and laboratory data for pooled nucleoside-naïve subjects and pooled LVD-refractory subjects. Pooling safety data from Studies 022 and 027 and from Study 026 and the pertinent treatment arms of Study 014 allowed for larger numbers of patients in populations that were of similar stage of disease and treatment. The conclusion that the safety profile of ETV was comparable to that of LVD held up regardless of whether individual studies or pooled data were evaluated. For some subgroup analyses of AEs and laboratory abnormalities, all ETV and all LVD subjects were pooled in order to increase the sample size in the subgroups.

7.4.1.2 Combining data

In pooling data for this review, the numerator events or laboratory abnormalities and denominators for the selected studies were combined. No selective weighting of events or studies was performed as all studies were considered equally important. For the analysis of malignancies, all patients in the safety database were combined to provide the denominator.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The pivotal studies included ETV doses of 0.5 mg and 1 mg given once daily. The applicant did not conduct a formal evaluation comparing safety of these doses, however, there appeared to be no significant difference in the safety profile of ETV across this dose range.

7.4.2.2 Explorations for time dependency for adverse findings

Other than the exploration related to the timing of ALT flares, no formal evaluation of time dependency for adverse findings was conducted. For a description of the evaluation of ALT flares, refer to Section 7.1.3.3 Other significant adverse events.

7.4.2.3 Explorations for drug-demographic interactions

The applicant conducted subgroup analyses of clinical adverse events and laboratory abnormalities across the treatment arms. Although there were some differences based on different demographic parameters (gender, age, race, etc) these were generally comparable across the 2 treatment groups and did not appear to be drug-specific.

7.4.2.4 Explorations for drug-disease interactions

There was no formal analysis conducted to explore drug-disease interactions for ETV used in different stages of HBV. However, there were no significant differences in safety between the nucleoside-naïve population and the LVD-refractory population. All study subjects reported in the NDA safety data had compensated liver disease and a different safety profile or level of tolerance of ETV may be identified when subjects with decompensated liver disease are evaluated.

7.4.2.5 Explorations for drug-drug interactions

Because ETV is primarily excreted unchanged in the urine, few drug-drug interactions were anticipated. Subjects who required nephrotoxic drugs as part of their treatment were prohibited from enrolling in the pivotal studies. As part of Study 015, the pilot study in liver transplant recipients, the applicant evaluated the PK profile of ETV in small numbers of subjects who were receiving cyclosporine or tacrolimus. For more information regarding this study, refer to the Clinical Pharmacology/Biopharmaceutics review conducted by Dr. Kim Bergman.

7.4.3 Causality Determination

The safety profile of ETV was similar to that of LVD in each of the 4 pivotal studies and in pooled nucleoside-naïve subjects and LVD-refractory subjects. AEs were commonly reported but there were few differences in the pattern of AEs reported by ETV-treated patients compared to LVD-treated patients. Reported AEs were also comparable between nucleoside-naïve and LVD-refractory patients. Many of these events are common in the general population and in the population of patients with chronic HBV. Among the clinical and laboratory events most commonly considered drug-related were: headache, fatigue, nausea, abdominal pain, and abnormalities of ALT, AST, amylase, and lipase. It is very likely that these events are causally related to ETV (and LVD), however, without a long-term comparison of ETV to placebo in patients with chronic HBV it may be impossible to be certain of the exact contribution of ETV. At this time, a placebo-controlled long-term study of chronic HBV treatment would be considered unethical.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant seeks approval for treatment of chronic HBV at doses of ETV 0.5 mg once daily in nucleoside-naïve patients and ETV 1 mg once daily in LVD-refractory patients. The submitted pivotal studies support these doses.

There were no differences in drug exposure based on gender. Minor increases in ETV exposure in elderly subjects compared to younger subjects is most likely attributed to changes in renal function in that population and no specific age-related dose adjustments are necessary. Differences in ETV exposure in Asians and non-Asians are most likely attributable to differences in body weight and no dose adjustment based on race is necessary.

The once daily dosing interval is well-supported by the PK data submitted. Additionally, food effect studies suggest that ETV should be dosed on an empty stomach. It will be recommended that ETV be administered at least 2 hours before a meal and at least 2 hours after a meal. *In vitro* virologic data suggested that HBV harboring mutations associated with LVD resistance also had reduced susceptibility to ETV and this is reflected in the proposed dosing recommendations.

In Phase 2 studies of multiple doses, there was an exposure-response relationship between ETV exposure and decreases in HBV DNA levels. Because marked decreases in HBV DNA were observed in nucleoside-naïve subjects with a dose of ETV 0.5 mg and because there appeared to be a dose effect in terms of rates of pooled neurologic AEs, higher doses of ETV were not studied in the nucleoside-naïve population. The higher dose of ETV 1 mg was evaluated in LVD-refractory subjects and no increase in neurologic AEs was identified. In light of the potential for ETV to be a human carcinogen, it was not considered appropriate to increase the exposure to the drug in long-term dosing. Refer to Sections 5.3 Exposure-Response Relationships and 6.1.3 Study Design, for more complete discussion of dose selection. The Phase 3 clinical trials clearly support the efficacy, safety, and tolerability of ETV compared to LVD in both nucleoside-naïve and LVD-refractory populations.

The applicant evaluated ETV exposure in subjects with renal impairment including those requiring hemodialysis and continuous ambulatory peritoneal dialysis (CAPD). 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 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 shown in the following table.

Table 8.1A: Proposed Dose Adjustments for Entecavir in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Nucleoside-naïve (0.5 mg)	LVD-Refractory (1 mg)
≥50	0.5 mg once daily	1 mg once daily
30 to <50	0.25 mg once daily	0.5 mg once daily
10 to <30	0.15 mg once daily	0.3 mg once daily
Hemodialysis* or CAPD	—	—

*Administer after hemodialysis.

Dr. Jenny H. Zheng, Clinical Pharmacology/Biopharmaceutics reviewer, confirmed the modeling and simulation results but concluded that the applicant's proposal for dosing patients requiring hemodialysis or CAPD would result in ETV exposure much higher than the proposed target. She suggested decreasing the recommended ETV dose in this group of patients to 0.05 mg for nucleoside naïve patients and 0.1 mg for LVD-refractory patients. The dose recommendations for patients with renal impairment will require use of the ETV oral solution (0.05 mg/mL) but should be simple to accomplish with this formulation.

8.2 Drug-Drug Interactions

No specific ETV drug-drug interactions are anticipated based on its metabolism. Since it is not extensively metabolized in the liver, it is unlikely to interact with drugs utilizing the cytochrome P450 system. It is not a substrate for p-glycoprotein and is also unlikely to compete with drugs utilizing this transporter system. There are no significant interactions between ETV and the other approved drugs for chronic HBV (LVD and ADV) in Phase 1 studies or the other nucleoside analogues used to treat HIV (abacavir, didanosine, LVD, stavudine, tenofovir, or zidovudine) in *in vitro* studies.

8.3 Special Populations

As noted above, the applicant evaluated ETV exposure in subjects with renal impairment including those requiring hemodialysis and CAPD. Specific dosage recommendations for patients with renal impairment are included in Section 8.1 Dosing Regimen and Administration.

ETV dosing was also evaluated in subjects with hepatic impairment and no significant differences in drug exposure were identified in this subgroup. Dose adjustment is not necessary in patients with hepatic impairment.

ETV has been studied in a small number of liver transplant recipients with recurrent HBV post-transplant. This study was too small to reach conclusions regarding the efficacy and safety of ETV in this population. However, no specific safety concerns were raised by the data available

from this cohort of subjects and decreases in HBV DNA were documented. However, PK determinations in this pilot study suggest that in HBV subjects post-liver transplant, mean ETV exposure was approximately twice that of healthy subjects following 14 days of oral 1 mg ETV. This increase in drug exposure in liver transplant recipients was consistent with the degree of renal impairment in these subjects. Based on this limited information, no dose adjustment (other than that for renal function) is suggested in liver transplant recipients should they need to receive ETV.

Recommendations for dosing in
are based on the results of Study 038. As for a dose of ETV

No pharmacokinetic evaluations were conducted during this study but the selected dose clearly had a beneficial effect on HBV DNA levels after 24 weeks of dosing compared to placebo. No specific safety concerns were raised in this cohort of subjects. This study is still ongoing and additional data will be available through another 24 weeks of open-label dosing.

The clinical trials did not assess ETV in women who were pregnant or breastfeeding. The animal reproductive toxicology studies suggest that there is a large margin of safety in administering ETV to pregnant animals. In the post-marketing stage, it is very likely that ETV will be taken by women who may be or may become pregnant while receiving the drug. The applicant has made arrangements to participate in a national prospective registry for pregnant women who receive treatment for HIV (the Antiretroviral Pregnancy Registry). This seems appropriate since many of the antiretroviral drugs are nucleoside analogues and both of the other drugs approved for treatment of HBV are included in the registry.

8.4 Pediatrics

To date, the use of ETV for the treatment of chronic HBV in pediatric patients has not been evaluated. 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.

After the results of the rodent carcinogenicity studies were reported, the Review Team asked BMS to delay its pediatric development program. The impact of the carcinogenicity studies on pediatric development of ETV was discussed with the Pediatric Implementation Team (PdIT) at a meeting held on August 27, 2003. At that meeting it was decided that the pediatric development plan for ETV should remain inactive. We proposed that pediatric development could proceed when 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.

Now that the review of the data submitted in the NDA confirms that ETV is clearly superior to LVD by many efficacy measures and the general safety and tolerability profile is comparable, we believe the applicant should proceed with a pediatric development plan. A liquid formulation has already been developed and will be approved based on the need for significant dose

adjustments in adults with renal impairment. It is imperative to obtain PK, safety, and efficacy data in pediatric patients as quickly as possible since the liquid formulation will be available.

8.5 Advisory Committee Meeting

On March 11, 2005, the Advisory Committee of the Division of Antiviral Drug Products met to review the use of ETV for the treatment of chronic HBV in adults. The committee heard presentations from the applicant and the Review Team describing the animal carcinogenicity findings, the clinical safety, efficacy, and resistance profile of ETV, and outlining the applicant's post-marketing pharmacovigilance proposals. The primary goal of the committee was to determine the risk-benefit of ETV in the context of the available clinical safety, efficacy, and resistance data and the pre-clinical animal carcinogenicity findings. The committee was also asked to provide advice on potential risks and benefits of proceeding with development of ETV for the treatment of chronic HBV in pediatric patients, the appropriateness of the applicant's proposed pharmacovigilance plan to address clinically relevant issues, and any other issues that should be addressed in post-marketing commitments.

During the discussion, the committee agreed that the efficacy and safety of ETV as determined by the Phase 3 clinical trials outweighed the potential unknown risk of cancer. The committee members commented that the benefits identified in the first 48 weeks of dosing in these studies might result in substantial clinical improvement and delay or prevent the emergence of complications of chronic HBV (cirrhosis, need for liver transplantation, HCC, and death). They viewed the risk posed by the animal carcinogenicity studies to be "hypothetical" while the risk of complications of untreated HBV is "real." The committee voted unanimously to approve ETV but also agreed that long-term follow-up to track cancer risk and emergence of resistance was necessary. The committee agreed that development of the drug for pediatric patients with chronic HBV should proceed and that PK data should be obtained expeditiously to limit the inappropriate and potentially dangerous off-label use of the drug in this age group. Finally, the committee agreed that the proposed post-marketing study would be an appropriate vehicle to track cancer risk as ETV is used in a larger population. It was also suggested during the Advisory Committee meeting that the applicant should include in the protocol design of the post-marketing study an early determination of adequacy of enrollment and have a plan to convert to a non-randomized cohort study if there seems to be hesitation to enroll in a randomized study. The committee discussed the need for additional post-marketing commitments to better evaluate the durability of response to ETV, to consider studies in subjects with chronic HBV but normal ALT levels, and to evaluate the response to ETV treatment in patients with decompensated liver disease and/or renal failure.

8.6 Literature Review

Other than the literature review provided by the applicant with the NDA, no specific literature review was conducted.

8.7 Postmarketing Risk Management Plan

In order to further assess the risk of cancer and serious hepatic related events in patients receiving ETV, the applicant has proposed a comprehensive pharmacovigilance plan for ETV. This plan includes increased monitoring and analysis of post-marketing safety reports and regular reporting of the results to the FDA. BMS has agreed to submit Periodic Safety Update Reports (PSURs) every 6 months for the first 5 years of marketing as well as Periodic Adverse Drug Event Reports (PADERs) every 3 months for the first 3 years of marketing. A summary and analysis of reported malignancies, serious hepatic events, and post-treatment exacerbations of hepatitis from ongoing clinical trials, observational studies, and spontaneous reporting will be included every 6 months in the PSUR.

The pharmacovigilance plan also includes continued tracking of subjects completing the clinical trials through the ongoing rollover and observational studies. Studies 901 and 049 will obtain data on long-term ETV dosing ($\geq$ 5 years for subjects in 901) and follow-up off ETV ($\geq$ 5 years for subjects in 049) for patients rolled over from the Phase 2 and 3 clinical trials to address the following issues: maintenance of virologic suppression, durability of HBeAg seroconversion and the rate of new events, risk of drug-related adverse events including malignancy, and risk for development of resistance to entecavir. To date, the applicant has enrolled a very high proportion of subjects completing other clinical trials into one of these rollover protocols.

Finally, BMS has proposed a large simple safety study to evaluate the occurrence of major events as ETV moves into broader clinical use. This study is designed as a randomized, open-label, cohort study planned to enroll about 12,500 patients $\geq$ 16 years of age. Patients will be randomized 1:1 into the ETV group or a standard of care group. Patients in the standard of care group could receive any anti-HBV nucleoside or nucleotide chosen by their physician. Patients will be stratified according to prior treatment with nucleosides. Major exclusion criteria include decompensated liver disease, history of or current treatment for cancer, and prior treatment with ETV. Patients will be followed annually for 5 years after the last patient is enrolled and follow-up will continue until the patient dies or is lost to follow-up. Patients will remain in their originally assigned group for analysis regardless of later discontinuation or switch in treatment. Data will be gathered primarily from medical records and questionnaires. The outcomes to be analyzed will include all cause and cause-specific mortality, liver transplantation, and malignancy (all cancer, HCC, and non-liver cancer). The applicant proposes that the study will be monitored by an independent Data Safety Monitoring Board and that interim analyses will be submitted to the FDA.

While we have not yet received a final study protocol for the post-marketing safety study, we have reviewed the draft protocol and discussed the proposal with our colleagues in the Division of Drug Risk Evaluation (DDRE). A summary of the DDRE consult is included in Section 8.8 Other Relevant Material. The proposed study has a number of strengths and represents a good effort on the applicant's part to collect important safety data. Among the study's strengths are a study design that includes randomization, an active control group, stratification by prior treatment, pertinent endpoints, and planned analyses. It will evaluate an international patient population who are using the drug in "real-life" settings. The study will allow enrollment of

patients with concomitant HCV and HIV and a broader spectrum of patients with chronic HBV than was seen in the clinical trials. The size of the study, 12,500 patients, and enrollment through many local physicians each following a relatively small number of their own patients may be advantageous.

However, the proposed study also has potential limitations that must be acknowledged. The length of the study may not be adequate to identify malignancies with a long latency and some mechanism for ascertaining events over a longer period may be useful. In this case, no specific tumor type can be targeted for surveillance. Results may be confounded as subjects switch from their original assigned treatment to the comparator group. It is certainly possible that the number of patients lost to follow-up may be higher than anticipated. There is no way to stratify for all the possible co-factors for malignancy that might be encountered in the population or patients' different level of risk for HCC based on their disease history. Finally, and most importantly, negative findings at the end of the study may not equate to a conclusion that there is no risk.

Given the pros and cons of initiating and conducting this type of large cohort study, the Review Team considered this the best method for evaluating the potential cancer risk of ETV and will work with the applicant to evaluate the final protocol from a regulatory perspective and review any interim study results as they are submitted.

Although no specific hazard has been identified for pregnant women who might use ETV, the applicant has proposed to encourage prospective reporting of ETV-treated pregnant women to a national pregnancy registry. They have received approval to list ETV in the Antiretroviral Pregnancy Registry, the registry initially established to track the outcomes of pregnancies of women who receive treatment for HIV. This registry is considered appropriate for tracking ETV-related pregnancy outcomes since, like many of the antiretroviral drugs, ETV is a nucleoside analogue and since it may be used in women who are co-infected with HIV and HBV. Both LVD and ADV are already listed in the Antiretroviral Pregnancy Registry. The registry's toll-free phone number will be included in the ETV label.

8.8 Other Relevant Materials

As part of the Review Team's assessment of the applicant's proposed pharmacovigilance plan, a formal consult was requested so that the reviewers and management in DDRE could comment on the plan. The formal consultation was accompanied by informal discussions between DDRE and the Review Team primarily regarding the proposed large, simple, safety study. These discussions and examples of post-marketing studies proposed for evaluation of cancer risk for other drugs were extremely useful in putting the ETV animal carcinogencity findings and post-marketing proposal into context. The completed consult written by Dr. Kate Gelperin is included in the NDA Action Package and will be briefly summarized below.

The DDRE consultant concluded that the proposed pharmacovigilance plan and post-marketing study have the potential to provide important information about the cancer risks and longer-term benefits and risks of ETV in an actual use setting in a diverse population. As proposed, the study

will only provide information over the 5 to 8 year period of observation and treatment and this may be too short a time to detect all cancer risk. Although sample size calculations have not been verified by FDA statisticians, the proposed study design is based on an ability to detect an increase in all cancers of 30% or a decrease in HCC of about 30%. A smaller increase in cancer risk or decrease in HCC risk may be clinically relevant but may not be detected. The study may be limited by not only the duration of follow-up but also the heterogeneity of the population enrolled with regard to risk of HCC, switching of patients into the alternate treatment group, and the local differences in ascertainment of cancers. In this setting, a failure to detect an adverse effect of ETV does not necessarily imply that there is none but it may provide some reassurance about the magnitude of a potential adverse effect and also about the overall risk-benefit of the drug.

DDRE agreed that this type of study was likely to provide the most useful cancer risk data over the proposed timeframe. The consultant suggested that some mechanism, such as a passive surveillance system extending beyond the formal annual data collection, be included to capture adverse events out through 10 years of follow-up. Also, DDRE suggested that separate analyses should be conducted for treatment naïve and treatment experienced patients entering the study with separate sample size requirements for each group. Analyses should include calculation of event incidence beyond the 25,000 person-year of exposure endpoint proposed in the draft protocol to be repeated in 5000 person-year increments through the recommended passive surveillance portion of the study. Details of the study design and statistical analyses will be discussed in more depth when the final protocol is submitted.

9 OVERALL ASSESSMENT

9.1 Conclusions

The FDA Clinical and Statistical Reviewers concluded that in well-conducted, multinational, studies in key subgroups of patients with compensated liver function, ETV was safe and effective in the treatment of adults with chronic HBV infection and evidence of ongoing liver inflammation. The data collection, study cohorts, selection of endpoints, and efficacy and safety analyses were adequate and appropriate to make the conclusion that ETV is safe and effective when used for its indicated purpose over 48 weeks of dosing.

Independent FDA review confirmed the conclusions submitted by the applicant and differences in efficacy analysis results were minimal and clinically insignificant. Analysis of the study results confirmed that ETV was superior to LVD in achieving the primary endpoint of overall histologic improvement in each of the 3 Phase 3 studies enrolling different important patient populations. Sensitivity analyses conducted by both the applicant and the FDA Statistical Reviewer supported the robustness of these results. Similarly, the treatment effect measured by the primary efficacy endpoint was observed consistently across subgroups based on gender, race, age, geographic region, and a variety of baseline disease covariates.

Review of key secondary endpoints also supported the efficacy of ETV compared to LVD. ETV was shown to be superior to LVD in all analyses evaluating changes in HBV viral load over 48 weeks regardless of which HBV DNA assay was used (bDNA or PCR). FDA review confirmed the applicant's conclusions that a greater proportion of ETV subjects than LVD subjects achieved HBV DNA < 400 copies/mL and ETV subjects achieved greater mean decreases in HBV DNA by PCR. Virologic responses were superior for ETV-treated subjects compared to LVD-treated subjects in all of the Phase 3 studies. Other key secondary endpoint analyses concluded that ETV was superior or equivalent to LVD through 48 weeks for the proportion of subjects achieving normalization of ALT (depending on method of calculating ALT normalization and study) and the proportion with improvement in Ishak fibrosis score (depending on study).

A supportive study conducted in HIV/HBV co-infected subjects demonstrated that in patients receiving LVD as part of the HIV therapy and LVD-refractory HBV, ETV had a significant effect on HBV replication as measured by HBV DNA levels through 24 weeks of dosing. A small proportion of these co-infected subjects achieved HBV DNA < 400 copies/mL by Week 24 and a relatively small proportion achieved normalization of ALT. Although the study design of the study in HIV/HBV co-infected subjects was different from the other studies conducted in LVD-refractory subjects, it appeared that this population achieved virologic results that were not quite as robust as those achieved by non-HIV-infected subjects.

The Review Team considers any review of a drug's antiviral efficacy must include an understanding of the development of resistance to the drug. The applicant conducted extensive resistance testing of HBV isolates to ETV during the pivotal studies. The major conclusions confirmed by the FDA virologists include several key points. No ETV resistance has been detected in ETV-treated nucleoside-naïve patients at 48 weeks but longer term data are needed to determine what mutations will emerge on ETV treatment and to determine the ETV resistance pathway in naïve subjects. ETV resistant mutations can emerge on ETV treatment when LVD mutations are present and emerge at a frequency of <10% at 48 weeks. Substitutions at amino acids I169, T184, S202 and M250 of the HBV polymerase are associated with ETV resistance both individually and in combination but, to date, these ETV-associated resistance substitutions emerged only when LVD-resistant mutations at L180 and/or M204 were present at baseline. These ETV resistant mutations were associated with virologic rebound. Finally, ETV is cross-resistant with LVD but not ADV in *in vitro* testing.

Independent FDA review concluded that the safety profile of ETV was similar to that of LVD in each of the 4 pivotal studies and in pooled nucleoside-naïve subjects and LVD-refractory subjects. AEs were reported frequently in the nucleoside-naive patients (about 81% in both arms) but there were few differences in the pattern of AEs reported by ETV-treated patients compared to LVD-treated patients. The pattern of commonly reported AEs was very similar in the LVD-refractory patients, with 85% of ETV subjects and 82% of LVD subjects reporting some AE. The most commonly reported events in ETV-treated subjects included: headache, upper respiratory infection, nasopharyngitis ("common cold"), fatigue, cough, abdominal pain, and arthralgia. Many of these events are common in the general population and in the population of patients with chronic HBV. Most of the reported AEs in both treatment groups were mild in

intensity and considered unrelated to study drug. Relatively few AEs of moderate to severe intensity were considered drug-related in either treatment group. Among those most commonly considered drug-related were: headache, fatigue, nausea, abdominal pain, and clinically significant abnormalities of ALT, AST, amylase, and lipase. Many of these events were numerically more frequent in LVD-treated subjects than ETV-treated subjects.

Three categories of adverse events deserve increased attention because of either the potential seriousness of the events or signals from animal toxicology studies: acute exacerbations of hepatitis (ALT flares), nervous sytem/neurologic AEs, and malignancies. To date, none of these events has been shown to occur more frequently among ETV-treated subjects compared to LVD-treated subjects.

During the ETV development program, ALT flares were tracked both during treatment and off-treatment follow-up using a standardized definition, the occurrence of ALT values at least 2 x the subject's baseline value and 10 x the ULN. ALT flares were documented infrequently in nucleoside-naïve patients during the on-treatment period but occurred more often in subjects receiving LVD (2% ETV vs 4% LVD). Compared to on-treatment, ALT flares occurred slightly more frequently in the off-treatment follow-up period in both treatment groups but were again documented more often among LVD subjects (4% ETV vs 8% LVD). ALT flares were documented more often among patients in the LVD-refractory trials. In this population, 2% ETV subjects and 10% LVD subjects experienced ALT flares while receiving study drug and 6 LVD patients discontinued study drug because of ALT flares. The number of LVD-refractory subjects followed off-treatment was too small to make definitive conclusions regarding rates of ALT flares in this setting.

Nervous system toxicity was identified in one of the animal toxicology studies and there appeared to be a dose-response relationship for these events identified in the Phase 2 studies. Grouped and individual neurologic AEs were evaluated in each of the pivotal studies and for the pooled nucleoside-naïve subjects and pooled LVD-refractory subjects. Rates of all neurologic events were similar across treatment groups in both nucleoside-naïve and LVD-refractory subjects. There were no significant differences in the proportions of subjects reporting anxiety, dizziness, headache, insomnia, migraine, paresthesia, somnolence or syncope across treatment groups. No significant pattern of ETV-related neurologic AEs could be identified. These events will continue to be evaluated in the ongoing Phase 3 studies and other clinical trials assessing long-term dosing of ETV.

The occurrence of malignancies during ETV use was of special interest during the review process because of the rodent carcinogenicity study findings and because chronic HBV is known to be a strong risk factor for development of HCC. A review of all cases of malignancy reported during the ETV development program identified 37 subjects with malignancies. Of these subjects 28 were in the randomized clinical trials populations: 19/1497 ETV subjects (1.3%) and 9/899 LVD subjects (1%). Nine subjects were in special study populations (decompensated, HIV/HBV co-infected, or receiving dual therapy): 3 receiving ETV alone, 2 receiving ADV alone, and 4 receiving combination therapy with ETV+LVD. The most commonly reported malignancy was HCC, occurring in 9 ETV, 4 LVD, and 2 ADV subjects. Other malignancies

occurring in more than one subject included: gastric carcinoma, basal cell carcinoma, prostate cancer, and breast cancer. 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 subject received study drug for over a year but even this is a relatively short reporting period for assessing carcinogenic potential.

The applicant calculated the rates 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. 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. The applicant continues to track malignancies in all of the ongoing clinical trials and will further assess longer-term cancer risk with a proposed post-marketing safety study.

9.2 Recommendation on Regulatory Action

The Medical Officers completing the Clinical Review of ETV recommend that ETV be approved for the treatment of chronic HBV in patients with evidence of

/. This recommendation is based on review of the efficacy and safety data submitted by Bristol-Myers Squibb. No deficiencies were identified in the NDA submission that would preclude approval.

Several issues must be considered in determining the overall risk-benefit of ETV in the treatment of chronic HBV and how ETV 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 human subjects, has few significant drug-drug interactions, and dosing can be reasonably adjusted in subjects with impaired renal function using the oral solution formulation. ETV effectively reduces the HBV viral burden and leads to improvement in liver histology and normalization of liver transaminases in subjects receiving the drug for 48 weeks. It achieved these endpoints in a greater proportion of subjects than did LVD in both nucleoside-naïve patients and LVD-refractory cohorts. 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. 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.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The applicant has proposed a comprehensive pharmacovigilance program that will address the issues of cancer risk and serious hepatic adverse events following the approval of ETV. This proposal is outlined in Section 8.7 Postmarketing Risk Management Plan and has been discussed with both the Review Team and DDRE.

BMS has agreed to submit Periodic Safety Update Reports (PSURs) every 6 months for the first 5 years of marketing as well as Periodic Adverse Drug Event Reports (PADERs) every 3 months for the first 3 years of marketing. A summary and analysis of reported malignancies, serious hepatic events, and post-treatment exacerbations of hepatitis from ongoing clinical trials, observational studies, and spontaneous reporting will be included every 6 months in the PSUR. The pharmacovigilance plan also includes continued tracking of subjects completing the clinical trials through the ongoing rollover and observational studies, Studies 901 and 049. These studies will address the following issues: maintenance of virologic suppression, durability of HBeAg seroconversion and the rate of new events, risk of drug-related adverse events including malignancy, and risk for development of resistance to entecavir.

The applicant has proposed a large simple safety study to evaluate the occurrence of major events as ETV moves into broader clinical use. This study is designed as a randomized, open-label, cohort study planned to enroll about 12,500 patients $\geq$ 16 years of age, randomized to receive either ETV or standard of care group (any anti-HBV nucleoside or nucleotide chosen by their physician). Data will be gathered primarily from annual review medical records and annual questionnaires. The outcomes to be analyzed will include all cause and cause-specific mortality, liver transplantation, and malignancy (all cancer, HCC, and non-liver cancer). The applicant proposes that the study will be monitored by an independent Data Safety Monitoring Board and that interim analyses will be submitted to the FDA. While we have not yet received a final study protocol for the post-marketing safety study, we have reviewed the draft protocol, discussed the proposal with our colleagues in DDRE, and agree that the proposed study represents an appropriate effort on the applicant's part to collect important safety data. Strengths and limitations of the study have been discussed internally and with the applicant. The Review Team, DDRE, and the applicant will discuss details of the study design and statistical analyses when the final study protocol is submitted later this year.

Finally, BMS has proposed to track the outcomes of pregnant women who receive treatment with ETV through the mechanism of the established Antiretroviral Pregnancy Registry. This

approach is considered appropriate by the Review Team and the registry's toll-free phone number will be included in the ETV label.

9.3.2 Required Phase 4 Commitments

The applicant has agreed to a series of post-marketing commitments designed to provide additional information regarding the durability of response to treatment with ETV, efficacy and safety in additional key patient populations including children, development of resistance in different patient populations, long-term risk of cancer, and the occurrence of significant hepatic complications. Under the Pediatric Research Equity Act we are deferring pediatric studies of ETV. Phase 4 commitments #8 and #9 will fulfill the requirements of PREA. As pediatric development of ETV progresses, a reevaluation of the need for studies in children < 2 years of age will be conducted. The Phase 4 commitments are detailed below.

1. Conduct and submit a final study report for a large simple safety study to assess the major clinical outcomes of death, progression of liver disease, and cancer in a broad population of HBV-infected patients using entecavir compared to standard of care over a period of 5 to 10 years of follow-up. The study should be randomized, stratified according to prior treatment, and of sufficient size to detect a 30% difference in cancer outcomes between the 2 groups. Monitoring by an independent Data Safety Monitoring Board is recommended. Given the anticipated length of the study, it is recommended that the protocol will include plans to assess the adequacy of enrollment and submit interim reports of results at yearly intervals.
Protocol submission: July, 2005
Final report submission: July, 2016

2. Complete and submit the final study report for Study 048 comparing the efficacy and safety of entecavir to adefovir in patients with chronic HBV and decompensated liver disease.
Protocol submission: study ongoing
Final report submission: October, 2008

3. Conduct and submit a final study report for a larger efficacy and safety study of entecavir in patients who are post-liver transplant. This study should enroll 50 to 100 patients and include analysis of virologic, biochemical, and serologic endpoints, evaluation of safety, and evaluation of HBV resistance.
Protocol submission: December, 2005
Final report submission: December, 2008

4. Complete and submit the final study report for Study 038 evaluating the safety, efficacy, and resistance profile of entecavir in patients with HIV/HBV co-infection.
Protocol submission: study ongoing
Final report submission: July, 2006

5. Complete and submit the final study reports for Studies 022, 027, and 026 and evaluate the safety and efficacy of entecavir compared to lamivudine during the second year of continued blinded study drug dosing.

Protocol submission: studies ongoing
Final report submissions: October, 2006

6. Complete and submit the final study reports for Studies 901 and 049 to obtain long-term dosing (≥ 5 years for some subjects) and follow-up (≥ 5 years for some subjects) on entecavir use in patients rolled over from the Phase 2 and 3 clinical trials to address the following issues:

- maintenance of virologic suppression
- durability of HBeAg seroconversion and the rate of new events
- risk of drug-related adverse events including malignancy
- risk for development of resistance to entecavir

Protocol submission: studies ongoing
Final report submission: July, —

7. Continue to perform genotypic and phenotypic analyses of HBV DNA from patients receiving long-term entecavir therapy in ongoing clinical trials 022, 027, 026, 038, 048, and 901. Provide 96-, 144-, and 240-week data on the genotypic and phenotypic analyses of isolates from entecavir-treated patients with chronic HBV who experienced virologic rebound in serum HBV DNA levels in both the nucleoside-naïve and lamivudine-refractory studies.
Protocol submissions: studies ongoing
Report submissions: Summary reports of overall consecutive resistance analyses submitted annually.

8. Conduct a study or substudy to determine entecavir exposure (PK profile) for pediatric patients from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.
Protocol submission: December, 2005
Final report submissions: July, 2007

9. Using doses selected based on study/substudy described in #8, conduct an efficacy and safety study of entecavir in pediatric patients from birth through 16 years of age with efficacy based on the results of a variety of virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.
Protocol submission: July, 2007
Final report submissions: December, 2009

10. Conduct and submit a final study report to evaluate the safety, efficacy, and resistance profile of entecavir used in combination with another oral anti-HBV therapy in treatment-naïve and treatment-experienced patients with chronic HBV to determine if there is any added benefit of combination therapy.
Protocol submission: December, 2005
Final report submission: December, 2009

11. Determine the in vitro susceptibility to ETV and ADV of substitutions at rtI169 alone and in the context of lamivudine- and ETV-associated resistance mutations and determine the in vitro

susceptibility to ETV of tenofovir-associated resistance substitutions at rtA194 in a lamivudine-resistant background.
Final report submission: July, 2006

12. Conduct and submit a final study report to evaluate the use of ETV in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (blacks/African Americans, Hispanics).
Protocol submission: December, 2005
Final report submission: December, 2008

9.3.3 Other Phase 4 Requests

At this time, there are no additional recommended or optional post-marketing commitments.

9.4 Labeling Review

The proposed package insert (label) has been reviewed by all disciplines involved in the NDA review of ETV. Labeling revisions for each section of the proposed label are described in the respective discipline reviews. The major recommendations for revisions to the clinical sections of the proposed label are itemized below. These changes have been discussed with and agreed upon by the applicant.

1. All products with activity against HBV require a boxed warning regarding the potential for severe acute exacerbations of hepatitis (flares). This warning should also be reproduced in the WARNINGS section of the label and additional information regarding rates of flares may be presented in the ADVERSE REACTIONS section. Wording for the boxed warning has been standardized for all products and should be as follows:

> "Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS)."

2. All nucleoside analogue products for treatment of chronic hepatitis B contain a boxed warning against lactic acidosis. Wording for this warning has been standardized and should be as follows:

> "Lactic acidosis and serve hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals."

3. In the INDICATIONS AND USAGE section, [redacted] should be removed. The indication for which ETV is receiving approval is as follows:

"Entecavir is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on histological, virological, biochemical, and serological responses after one year of treatment in treatment-naïve and lamivudine-resistant adult patients with HBeAg positive or HBeAg negative chronic HBV with compensated liver disease and more limited data in adult patients with HIV/HBV co-infection."

4. In the Description of Clinical Studies section, we recommend that the applicant include only the 3 Phase 3 studies (022, 027, and 026) and a brief description of Study 038 in HIV/HBV co-infected subjects. The safety data from the relevant cohorts of Study 014 should be included in tables of safety data as currently described and/or in a table footnote.

5. In the Description of Clinical Studies section, all discussion of post-48 week management should be moved into a single section headed ' — Streamline the description of Week 52 management decisions for the 3 studies since they are similar. Limited information regarding this study endpoint should be included since this is not a recommended algorithm for HBV management. Include a caveat that these protocol-mandated management guidelines are not intended as clinical practice guidelines.

6. In all tables displaying efficacy data, delete the columns containing — and include as footnotes p values indicating where significant differences were found.

7. In tables displaying secondary endpoints, delete the rows displaying results — as these add little to the interpretation of study efficacy, remove the results of —, and delete the footnote containing —

8. In the Description of Clinical Studies section, delete the paragraphs describing the —. These represent a secondary endpoint analyses of assessments available only for research purposes.

9. In the description of Study 038, identify that there are no data in HIV/HBV co-infected subjects who have not received prior LVD and —

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10. In the PRECAUTIONS section, include a new subsection headed "Use in Racial/Ethnic Groups" and insert the following statement:

"Clinical studies of entecavir did not include sufficient numbers of subjects from some racial/ethnic minorities (black/African American, Hispanic) to determine whether they

respond differently to treatment with the drug. There are no significant racial differences in entecavir pharmacokinetics."

11. In displaying the laboratory abnormalities, re-title the table, "Selected — — . reported — in four entecavir clinical trials". Delete the rows — baseline." Include in the table proportions of subjects with Grade 3 or 4 laboratory toxicity for ALT, AST, amylase, lipase, creatinine (include both ≥ Grade 3 and ≥ 0.5 mg/dL above baseline), hyperglycemia, total bilirubin, urine glucose (glycouria), and urine blood (hematuria). Include the cut-off values for Grade 3 toxicity for each parameter. It is acceptable to display the proportion of subjects whose toxicity grade increased from baseline to a Grade 3 or 4.

12. In ADVERSE REACTIONS, delete the subsection " ," and incorporate this information into the introductory paragraph of the section. For example, "The safety profile of entecavir 1 mg (n=51) in HIV/HBV co-infected subjects enrolled in Study 038 was similar to that of placebo (n=17) through 24 weeks of blinded treatment and similar to that seen in non-HIV infected patients."

13. In the DOSAGE AND ADMINISTRATION, Recommended Dosage section, revise the wording of the first paragraph as follows:

"The recommended dose of entecavir for chronic hepatitis B virus infection in nucleoside treatment-naïve adults and adolescents older than 16 years of age is 0.5 mg once daily.

The recommended dose of entecavir in adults and adolescents with — .a — is 1 mg once daily."

14. Correct the dosing recommendations for patients with renal impairment requiring dialysis as agreed in the applicant's communication dated March 14, 2005.

15. In the Duration of Therapy section, revise the section to read:

"The optimal duration of treatment with entecavir for patients with chronic hepatitis B and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are not known."

16. In the Patient Package Insert, include information about lactic acidosis and ALT flares since these are now presented in a boxed warning in the label. Also, in the section, "What are the possible side effects of Baraclude?" include a statement regarding possible worsening of liver and pancreas-related blood tests. Additional comments regarding the PPI will be forwarded from the staff in the Division of Surveillance, Research, and Communication Support (DSRCS).

For a complete line-by-line listing of all changes in the final label, refer to the Project Manager's review of final printed labeling conducted by Marsha Holloman, Consumer Safety Officer, and included in the NDA Action Package.

The Proprietary Name Review has been completed and Baraclude™, the proposed trade name for ETV, was found acceptable by the staff in the Division of Medication Errors and Technical Support. A copy of the full DMETS consult is included in the NDA Action Package. The DMETS consultant recommended minor revisions in the container labeling to reduce potential dosing errors. It was recommended that the —
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The Patient Package Insert has also been reviewed by the staff in DSRCS and comments have been forwarded to the applicant. A copy of this consult is included in the NDA Action Package.

9.5 Comments to Applicant

At this time, all comments pertinent to ETV labeling and Phase 4 commitments forwarded to the applicant are described in Sections 9.3 and 9.4 above. No other comments need be conveyed to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 AI463022: A Phase 3 study of the safety and antiviral activity of entecavir vs lamivudine in adults with chronic hepatitis B infection who are positive for hepatitis B e antigen

Protocol Study Design

AI463022 (Study 022) was a randomized, double-blind, placebo-controlled study of ETV 0.5 mg given once daily compared to LVD 100 mg given once daily in patients with confirmed chronic HBV infection who were HBeAg positive. The primary objectives of the study were to compare the proportion of patients in each treatment group who achieved histologic improvement in liver biopsy after 48 weeks of study treatment and to determine the safety profile of ETV over 52 weeks of dosing.

Study subjects were recruited through a worldwide network of investigators in North America, South America, Europe, and Asia. Inclusion in the study required that subjects be $\geq$ 16 years of age (or the minimum age of consent in each country) with chronic HBV infection documented by positive HBsAg over at least 6 months and positive e antigen. Subjects were required to have evidence of chronic hepatitis by liver biopsy within 52 weeks of randomization, HBV DNA $\geq$ 3 MEq/mL by bDNA assay, serum ALT $\geq$ 1.3 x ULN, and compensated liver function. Subjects could have no more than 12 weeks of prior nucleoside/nucleotide therapy for HBV but could have received IFN therapy. The last dose of any prior therapy was to be at least 24 weeks prior to randomization. Male and female patients were enrolled. Agreement to use appropriate contraception was stipulated in the protocol. Major exclusionary criteria were concomitant HIV, HCV, or HDV, evidence of significant organ dysfunction (other than elevated transaminases), pregnancy or breastfeeding, other types of liver disease, or a screening alpha fetoprotein > 100 ng/mL.

After randomization, subjects were randomized 1:1 and received blinded study drug for 52 weeks. ETV was supplied as 0.5 mg tablets. LVD was supplied as 100 mg capsules. Matching placebos were used for each of the active study components. Subjects were instructed to take their assigned study drug and placebo once daily at approximately the same time each day, preferably at bedtime. Study drugs were to be taken 2 hours before or 2 hours after food.

Study subjects were evaluated every 4 weeks during this first year of dosing and monitored for safety with a battery of clinical and laboratory assessments. Clinical AEs were recorded at each study visit throughout the study and graded according to severity using a toxicity grading system modified from the WHO guidelines. Clinical AEs were also evaluated by the investigator according to perceived relationship to blinded study drug (certainly, probably, possibly, not

likely, or not related). Serious AEs and deaths were also identified and recorded. Laboratory abnormalities were also graded according to the modified WHO toxicity guidelines.

Clinical management decisions at Week 52 were based on results of virologic and serologic studies performed at the Week 48 study visit. Complete Responders (HBV DNA by bDNA assay < 0.7 MEq/mL and loss of HBeAg) stopped study treatment and were followed every 4 weeks 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. Study subjects continuing blinded dosing in the second year were evaluated every 8 weeks through Week 96. Non-responders (HBV DNA by bDNA $\geq$ 0.7 MEq/mL) discontinued study treatment but were eligible for the rollover study or other available therapy.

The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved histologic improvement in their Week 48 liver biopsy. Histologic improvement was defined in the protocol as $\geq$ 2 point decrease in the Knodell necroinflammatory score and no worsening in the Knodell fibrosis score compared to the baseline biopsy. Liver biopsy results were determined by a single pathologist who was blinded to a given subject's treatment assignment and the temporal order of the biopsies.

Reviewer's Comments:
Use of a single, centralized reader for clinical trial liver biopsies has been discussed at a previous Advisory Committee meeting. It was concluded that histologic scoring should be centralized and blinded because of the subjective nature of the determinations. The pathologist contracted to provide histologic scoring for this study is the same individual utilized in previous registrational trials of ADV for chronic HBV and is widely considered to be the leading expert in the field.

In addition to the primary histologic endpoint, there were multiple secondary endpoints to be evaluated. These were to determine the proportion of subjects in each treatment group who achieved histologic, virologic, serologic, and composite milestones at Week 48. Among the most important of these were:

- Proportion of subjects with improvement in hepatic fibrosis from baseline to Week 48 as measured by the Ishak fibrosis score
- Reduction from baseline in covalently closed circular DNA (cccDNA)
- Proportion of subjects with HBV DNA by the bDNA assay below the LOQ
- Proportion of patients with loss of HBeAg
- Proportion of patients with seroconversion (loss of HBeAg and appearance of HBeAb)
- Proportion of patients with normalization of ALT (defined as < 1.25 x ULN)
- Proportions of patients achieving Complete Response or Partial Response
- Proportion of subjects with HBV DNA < 400 copies/mL by the PCR assay
- Refractoriness to therapy, defined as rising HBV DNA titer while on study drug after first achieving undetectable levels. Genotypic analysis was to be performed on these isolates.

- Durability of Complete Response during 24 weeks off therapy follow-up
- Complete Response after up to an additional 48 weeks of dosing for subjects with a Partial Response at 48 weeks

The applicant planned a 2-step evaluation of the efficacy endpoints. First, the non-inferiority of ETV to LVD was to be tested. If non-inferiority was established, the second step to determine superiority of ETV to LVD was to be conducted.
The primary safety endpoint was intended to be the proportion of subjects in each group who discontinued study drug because of an AE. Common AEs, SAEs, deaths, and laboratory abnormalities were tabulated and summarized. In addition, events of special interest such as exacerbations in liver transaminases (ALT flares), hepatic SAEs, neurologic events, and malignancies were to be summarized.

Amendments

The original protocol was finalized on December, 2000. Three protocol amendments were submitted after that time. Key revisions included in the amendments are summarized below.

Amendment 1 (December 10, 2001)
In response to the Review Team's recommendations, the applicant added additional measurements of HBV DNA by PCR assay at Week 24. At that time, clinicians were rapidly adopting the PCR assay as the most sensitive assay for monitoring patients with chronic HBV. The applicant also added collection of specimens for HBV subtype assay at baseline and a secondary objective to evaluate response to therapy according to subtype. Additional secondary histologic assessments were also included in the evaluations of baseline and Week 48 liver biopsies.

Amendment 2 (January 24, 2003)
Amendment 2 modified several important study procedures. It stated that subjects who discontinued study therapy before Week 48 should have all Week 48 procedures performed at the time of discontinuation including the recommended liver biopsy. It also specified that all subjects who discontinued study drug (not just Complete Responders) be followed off treatment every 4 weeks for 24 weeks. A secondary endpoint of improvement in hepatic fibrosis score measured by the Ishak scoring system was added. The secondary endpoint of refractoriness to therapy was deleted and replaced with an endpoint for Virologic Rebound, defined as ≥ 1 log increase in HBV DNA by bDNA from the nadir on treatment. Subjects meeting the criteria of Virologic Rebound were to have HBV DNA samples submitted for genotypic and phenotypic analysis. Patients who required additional therapy for HBV after participating in the study would be allowed to enroll in the open-label rollover protocol or a new ETV compassionate access program.

Amendment 3 (December 30, 2003)
Amendment 3 was submitted in response to the growing awareness that some patients receiving treatment for chronic HBV or those discontinuing active treatment were at risk for ALT flares

and severe hepatic AEs. This amendment required that investigators report ALT flares (defined as ALT > 2 x baseline and > 10 x ULN) with or without other accompanying laboratory abnormalities and any events suggestive of hepatic decompensation as SAE under the expedited reporting guidelines. The Dose Modifications section of the protocol was revised to provide investigators with increased flexibility to continue study drugs in the face of increased ALT/AST. At that point, the study had been in progress for about 2 years and this may have led to an increase in reporting of ALT flares as SAEs after the amendment compared to before the amendment. Treatment management for Partial Responders who experienced rebound of HBV DNA by bDNA assay during the second year of dosing (loss of response) was clarified to indicate that investigators could initiate alternative treatment or enroll the subject in the rollover or compassionate access program for ETV.

Post Hoc Changes

No significant post hoc changes in the study analyses were noted.

Study Results

Disposition

A total of 1056 subjects were screened for Study 022 from 25 countries. Of these, 715 subjects were randomized to receive study drug. A total of 341 subjects were screened but never randomized and received no study drug. Of these, 292 were described as failing screening because they "no longer met study criteria," 45 subjects "withdrew consent," 2 subjects were "lost to follow-up," and 1 subject each was not randomized because of "noncompliance" or "randomization closed."

Of the 715 subjects randomized in Study 022, 709 received at least one dose of study medication. Table 10.1.1A summarizes the disposition of study subjects after randomization and through the study data cut-off date of April 28, 2004. Slightly fewer subjects in LVD arm completed the first year of study dosing and significantly fewer continued dosing in the second year of the study. Fewer of the LVD subjects met the criteria for Partial Response, the criteria for continuing treatment (see Efficacy Section below). Of those who did enter the second year of dosing, a greater proportion of subjects receiving LVD failed to complete the second year (35% vs. 7%).

Table 10.1.1A: Disposition of Subjects in Study 022

Disposition of Subjects	ETV	LVD
All randomized	357	358
Never dosed	3 (1%)	3 (1%)
Received study drug	354 (99%)	355 (99%)
Did not complete first year of dosing	14 (4%)	34 (10%)
Adverse event	1	9
Death	0	2
Lost to follow-up	3	8
Noncompliance	2	4
Pregnancy	2	2
Subject no longer meets study criteria	0	4
Subject withdrew consent	6	5
Completed first year of dosing	340 (96%)	321 (90%)
Continued to second year of dosing	252 (71%)	190 (54%)
Did not complete second year of dosing	18 (7%)	67 (35%)
Adverse event	0	1
Lost to follow-up	2	2
Non compliance	1	0
Pregnancy	1	1
Subject no longer meets study criteria	0	7
Subject withdrew consent	7	2
Treatment failure/lack of efficacy	7	54
Completed second year of dosing	117 (46%)	67 (35%)
Entered/completed 24-week follow-up	135/81	132/77

Source: AI463022: Clinical Study Report, Table 8.1A, page 126.
AI463022 Clinical Study Report Addendum 01, Table 8.1A, 8.1B, pages 61, 62.

Demographics and Baseline Disease Characteristics

Patients were recruited from 127 study sites (each enrolling 1 to 36 subjects) representing the global population with chronic HBV. Treatment groups in Study 022 were similar in demographic profile and baseline HBV disease characteristics as shown in Tables 10.1.1B and 10.1.1C.

Table 10.1.1A: Demographic Data – Study 022

Demographic Characteristic	ETV	LVD	Total
All randomized	357	358	715
Received study drug	354	355	709
Male/Female (%)	78%/22%	74%/26%	76%/24%
Mean age in years (range)	35.2 (16-76)	34.8 (16-78)	35.0 (16-78)
Race			
Asian	205 (57%)	203 (57%)	408 (57%)
Black/African American	8 (2%)	8 (2%)	16 (2%)
Native Hawaiian/Pacific Islander	1 (<1%)	2 (<1%)	3 (<1%)
Other	3 (1%)	2 (<1%)	5 (1%)
White	140 (39%)	143 (40%)	283 (40%)
Geographic region			
Asia	174 (49%)	168 (47%)	342 (48%)
Europe	84 (24%)	90 (25%)	174 (24%)
North America	47 (13%)	55 (15%)	102 (14%)
South America	52 (15%)	45 (13%)	97 (14%)

Source: Medical Officer's review of the clinical datasets.

Reviewer's Comments:
The number of Black/African Americans enrolled in the study is clearly insufficient to determine either safety or efficacy of ETV in this population and is not representative of the proportion of chronic HBV patients in this racial group. The poor enrollment of this population was discussed with the applicant at the time of the pre-NDA meeting.

Table 10.1.1C: Baseline Disease Characteristics – Study 022

Baseline Disease Characteristic mean (median)	Entecavir (N = 357 randomized, N = 329 with histology)	Lamivudine (N = 358 randomized, N = 330 with histology)
ALT (IU)	141 (102)	146 (103)
AST (IU)	78 (57)	83 (57)

Total bilirubin (mg/dL)	0.9 (0.8)	0.8 (0.7)
Prothrombin time (sec)	12.9 (12.6)	13.0 (12.8)
HBV DNA by bDNA assay (MEq/mL)	1957 (671)	1988 (706)
HBV DNA by PCR assay (copies/mL)	7.57E+13 (1.91E+9)	9.57E+13 (2.08E+9)
Log10 PCR	9.6 (9.3)	9.7 (9.3)
Knodell necroinflammatory score	7.8 (9.0)	7.7 (8.0)
Knodell fibrosis score	1.7 (1.0)	1.7 (1.0)
Ishak fibrosis score	2.3 (2.0)	2.3 (2.0)

Source: Medical Officer's review of the clinical datasets.

Efficacy

For a complete review of the primary efficacy analysis and selected secondary analyses please see the Statistical Review conducted by Dr. Tom Hammerstrom. The discussion of efficacy included below is derived from his analyses, additional calculations performed by the Medical Officer, and the applicant's stated results.

Primary Efficacy Analysis

The primary efficacy endpoint for Study 022 was histologic improvement in the Week 48 liver biopsy compared to the baseline biopsy. Histologic improvement was defined as $\geq$ 2 point improvement in Knodell necroinflammatory score and no worsening in the Knodell fibrosis score. The applicant used as their primary analysis a modified ITT analysis that evaluated only subjects who had an adequate baseline biopsy with a Knodell necroinflammatory score ≥ 2 and counted subjects with a missing or inadequate Week 48 biopsy as treatment failures. Results of this analysis were confirmed by Dr. Hammerstrom during his statistical review of efficacy (see his review for detailed discussion).

In general, the applicant met the target goals for obtaining liver biopsy specimens in Study 022; 681 treated subjects had a baseline biopsy and 646 had a Week 48 biopsy. However, not all biopsy specimens were considered adequate in size or quality. A total of 561 subjects had adequate baseline and Week 48 biopsy specimens and had a baseline Knodell necroinflammatory score of ≥ 2 and thus were fully evaluable for the primary endpoint.

ETV was found to be superior to LVD in the primary efficacy endpoint using the applicant's analysis. The ETV group had fewer missing or inadequate Week 48 biopsies than the LVD group. The applicant notes that this discrepancy is accounted for primarily by the higher number of discontinuations prior to Week 48 in the LVD group. The

applicant performed additional analyses using different methods to calculate efficacy including a more conservative analysis using a non-completer = failure method with all randomized patients. This method counts all patients with missing or inadequate biopsy data at either baseline or Week 48 as treatment failures. This sensitivity analysis again showed that ETV was superior to LVD in achieving the primary endpoint of histologic improvement. These results are summarized in Table 10.1.1D below.

Table 10.1.1D: Histologic Improvement at Week 48 – Study 022

	Entecavir (N = 357 randomized)	Lamivudine (N = 358 randomized)
Primary endpoint analysis (using evaluable baseline biopsy)	N=314	N=314
Histologic improvement	226 (72%)	195 (62%)
No improvement	66 (21%)	74 (24%)
Inadequate biopsy Week 48	7 (2%)	17 (5%)
Missing biopsy Week 48	15 (5%)	28 (9%)
Proportion with improvement: Difference estimate (95% CI)	9.9 (2.6, 17.2) p = 0.0085	
Sensitivity analysis (using all randomized subjects)		
Histologic improvement*	228 (64%)	196 (55%)
No improvement	77 (22%)	87 (24%)
Inadequate baseline biopsy	12 (3%)	10 (3%)
Missing baseline biopsy	16 (4%)	18 (5%)
Inadequate Week 48 biopsy	8 (2%)	17 (5%)
Missing Week 48 biopsy	16 (4%)	30 (8%)
Proportion with improvement: Difference estimate (95% CI)	9.1 (1.9, 16.3) p = 0.01	

Source: AI463022: Clinical Study Report, Table 10.1.1A, page 149 and Table 10.1.1D, page 152.
*Includes improvement for subjects with baseline Knodell necroinflammatory score of 1 or 0 if Week 48 necroinflammatory score of 0 and no worsening of Knodell fibrosis.

The applicant conducted subgroup analyses of the primary endpoint according to multiple demographic and baseline disease characteristics. Each of these analyses was performed using their primary efficacy analysis methodology (modified ITT, non-completer = failure, patients with evaluable baseline biopsy). ETV maintained at least numerical superiority over LVD in all geographic regions (North America, South America, Europe, and Asia) although in some regions the number of patients was too small to show statistical significance. Among larger ($\geq$ 100 subjects) subgroups identified by possible HBV prognostic factors, ETV appeared to be superior to LVD: in subjects with ALT $\geq$ 2.6 x ULN, in male subjects, in non-Asian subjects, and in those with prior IFN use. In other subgroups (ALT < 2.6 x ULN, female, Asian, HBV subtype, IFN-naïve) ETV was numerically better than LVD but failed to achieve statistical superiority. Dr. Hammerstrom confirmed results of these subgroup analyses and concluded that ETV was

non-inferior to LVD in all subgroups evaluated and statistically superior in many subgroups.

Secondary Efficacy Analysis

The applicant conducted multiple secondary analyses of efficacy using histologic, virologic, serologic, and composite endpoints. The analyses of these endpoints used a similar modified ITT method with non-completer = failure based on patients with available baseline data. Some of these analyses are summarized in Table 10.1.1E below. In general, these results were confirmed by Dr. Hammerstrom in his statistical review and/or by this Medical Officer although not all of the applicant's secondary analyses were duplicated during the review process.

One of the additional histologic endpoints evaluated as a secondary endpoint was improvement in the Ishak fibrosis score, another well-accepted method of grading liver histology. In the analysis of this histologic endpoint, the proportions of subjects with improvement were similar in the ETV and LVD groups.

The secondary analyses verify that ETV provides superior virologic suppression of HBV compared to LVD over the first 48 weeks of study dosing as measured by either the HBV bDNA assay or the HBV PCR assay. Subjects receiving ETV experienced a greater decrease in mean HBV DNA by PCR than did those receiving LVD. Similarly, while the majority of subjects in both treatment groups achieved normalization of ALT over 48 weeks, the subjects receiving ETV achieved this endpoint slightly more frequently. Seroconversion was observed in a relatively small proportion of subjects in either arm and similarly there were relatively few subjects who achieved the protocol-defined Complete Response, a composite of HBV bDNA < LOQ and e antigen loss. More subjects receiving ETV than LVD met the Partial Response criteria and proceeded to the second year of blinded dosing and fewer ETV than LVD subjects met the Non-Response criteria and discontinued study drug for that reason.

Table 10.1.1E: Secondary Efficacy Endpoints – Study 022

	ETV (N = 354 treated)	LVD (N = 355 treated)
Improvement Ishak fibrosis score (≥ 1 point decrease)	39%	35%
Hepatic cccDNA (mean change from baseline)	-0.9 log copies/HGEq (N = 159)#	-0.7 log copies/HGEq (N = 146)
HBV DNA by bDNA < LOQ (< 0.7 MEq/mL)	91%*	65%
HBV DNA by PCR < LOQ (< 400 copies/mL)	69%*	38%
Log HBV DNA by PCR (mean change from baseline)	-7.0*	-5.5

HBeAg seroconversion (e antigen loss and e antibody gain)	21%	18%
Protocol-defined ALT normalization (< 1.25 x ULN)	78%*	70%
Complete Response (HBV bDNA < LOQ and e antigen loss)	21%	19%
Partial Response (HBV bDNA < LOQ but e antigen still positive)	70%*	46%
Non-Responders (HBV bDNA > LOQ)	5%*	26%

Source: AI463022 Clinical Study Report and AI463022 Clinical Study Report Addendum 01.
#Hepatic cccDNA analysis required biopsy at time of screening. Retrieval of archived biopsies, allowed for enrollment, not adequate for testing.
*Statistically significant difference between ETV and LVD favoring ETV.

Reviewer's Comments:
Minor differences between the applicant's and this reviewer's assessment of the proportions of subjects achieving HBV DNA < LOQ for the two assays could be accounted for by slightly different methods of calculating study visit windows and confirmation of < LOQ. For example, in the calculations of proportion of subjects with HBV DNA < 400 copies/mL through Week 48, this reviewer identified 72% of ETV subjects and 42% of LVD patients achieving the endpoint compared to the applicant's 69% and 38%, respectively. These differences in methods of calculation had no impact on the review conclusions.

The applicant chose their cut-off for normalization of ALT based on use of laboratory toxicity grading tables that set Grade 1 ALT toxicity at > 1.25 x ULN. The Review Team disagreed with this choice of ALT normalization and believed that true normalization of ALT should be calculated as < 1.0 x ULN. Our calculations of ALT normalization using the stricter criteria identified 69% of ETV subjects compared to 61% of LVD subjects achieving the endpoint. This more conservative calculation still favored ETV.

The applicant evaluated those subjects who discontinued blinded study drug after achieving a protocol-defined Complete Response. This population included 74/354 (21%) ETV-treated subjects and 67/355 (19%) LVD-treated subjects. The applicant notes that 71/74 ETV subjects and 60/67 LVD subjects discontinued study drug per protocol between 48 and 54 weeks with the remaining subjects discontinuing after Week 54. Among the responders, 61/74 (82%) ETV subjects and 49/67 (73%) LVD subjects maintained the Complete Response criteria through 24 weeks of off-treatment follow-up.

Safety

The applicant evaluated the safety of ETV compared to LVD in Study 022 by assessing clinical and laboratory events in all patients who received at least one dose of blinded study drug: 354 ETV subjects and 355 LVD subjects. They divided the safety analysis into three

periods. The on-treatment period includes all data from patients treated through the data cut-off (April 28, 2004). The off-treatment follow-up includes data from the 263 patients who discontinued blinded study treatment for any reason and had safety data while not receiving other HBV therapy. The 24-week follow-up includes all safety data collected after subjects discontinued blinded treatment regardless of whether they received other HBV therapy (excluding those enrolled in the BMS rollover protocol). As there were only 4 additional subjects in the 24-week follow-up compared to the off-treatment follow-up cohort, the FDA safety analysis included only the on-treatment and off-treatment follow-up periods.

Adverse Events

The applicant tabulated clinical AEs using preferred terms and system organ class designations as listed in MedDRA 6.1. In general, the Clinical Reviewers' analyses confirmed the applicant's summary of AEs reported during Study 022 in both on-treatment and off-treatment periods. Very minor discrepancies in rates of AEs could be attributed to slightly different methods of calculating the on-treatment period for each subject.

As might be expected for a population with a chronic underlying disease such as HBV infection, clinical AEs were reported frequently during the on-treatment and off-treatment periods. Combined non-serious and serious AEs were reported in 86% of ETV subjects and 85% of LVD subjects. These AEs did not emerge in a specific organ system as noted in Table 10.1.1F. Gastrointestinal events (47% compared to 39%) and respiratory/thoracic events (31% compared to 25%) were reported in slightly more ETV subjects than LVD subjects. Rash events were reported in slightly more LVD subjects than ETV subjects (6% compared to 3%). Nervous system toxicity was identified during the animal toxicology studies of ETV and was part of the basis for dose selection in nucleoside-naïve subjects. Subjects receiving ETV reported slightly more nervous system AEs than did LVD subjects (32% compared to 29%). These events will be evaluated in more detail later in the review.

Table 10.1.1F: Patients Reporting Selected Organ System Events in Study 022 (all grade, all causality) – On-Treatment

Organ System	Entecavir (N = 354)	Lamivudine (N = 355)
Cardiac disorders	9 (3%)	4 (1%)
Gastrointestinal disorders	166 (47%)	138 (39%)
Hepatobiliary disorders	6 (2%)	9 (3%)
Musculoskeletal and connective tissue disorders	74 (21%)	72 (20%)
Neoplasms benign, malignant, and unspecified	6 (2%)	7 (2%)
Nervous system disorders	115 (32%)	104 (29%)

Rash events (combined terms)	10 (3%)	22 (6%)
Renal and urinary disorders	24 (7%)	26 (7%)
Respiratory, thoracic and mediastinal disorders	108 (31%)	90 (25%)
Vascular disorders	14 (4%)	9 (3%)

Source: Medical Officer's review of the clinical datasets.

The most commonly reported clinical AEs in Study 022 regardless of treatment group included upper abdominal pain, diarrhea, fever, fatigue, headache, cough, upper respiratory tract infection, and nasopharyngitis (preferred term for "common cold"). Among the commonly reported AEs, cough, headache, pyrexia, rhinorrhea, and upper respiratory tract infection were observed slightly more often in ETV-treated subjects than LVD-treated subjects. Increased ALT was reported as a clinical AE in slightly more LVD subjects than ETV subjects. It is difficult to determine the significance of these observations in light of the multiple comparisons conducted in the safety analysis. Table 10.1.1G summarizes the AEs most commonly reported in patients while on treatment.

Table 10.1.1G: Adverse Events Reported in ≥ 5% of Patients On-Treatment in Study 022 (all grades, all causality)

Adverse Event (MedDRA 6.1 Preferred Term)	ETV (N = 354)	LVD (N = 355)
All patients with AE	306 (86%)	302 (85%)
Abdominal pain	31 (9%)	29 (8%)
Abdominal pain upper	39 (11%)	38 (11%)
ALT increased	19 (5%)	34 (10%)
Arthralgia	28 (8%)	23 (6%)
Back pain	23 (6%)	23 (6%)
Blood amylase increased	13 (4%)	18 (5%)
Cough	53 (15%)	44 (12%)
Diarrhea	39 (11%)	33 (9%)
Dizziness	29 (8%)	22 (6%)
Dyspepsia	22 (6%)	24 (7%)
Fatigue	39 (11%)	36 (10%)
Headache	87 (25%)	75 (21%)
Influenza	26 (7%)	25 (7%)
Myalgia	18 (5%)	19 (5%)
Nasopharyngitis	51 (14%)	54 (15%)
Nausea	25 (7%)	22 (6%)
Pharyngolaryngeal pain	24 (7%)	16 (5%)
Pyrexia	42 (12%)	30 (8%)
Rhinorrhea	20 (6%)	11 (3%)
Upper respiratory tract infection	77 (22%)	63 (18%)

Source: Medical Officer's review of the clinical datasets.

Although AEs were reported by the majority of subjects in both treatment groups, most of the events were graded as mild or moderate in severity. Grade 3 or 4 (severe or life-threatening) AEs were reported in 49/354 (14%) ETV subjects compared to 59/354 (17%) LVD subjects. Most of the Grade 3 or 4 events occurred in isolated cases. Grade 3 or 4 AEs occurring in more than 1% of either treatment group included: increased ALT (3% ETV, 6% LVD), increased AST (< 1% ETV, 2% LVD), and increased serum lipase (2% ETV, 1% LVD).

Similarly, most of the AEs reported during the on-treatment period in both treatment groups were considered by the investigators not to be related to study drug administration. Among ETV subjects 139 (39%) reported AEs considered possibly, probably, or certainly related to study drug compared to 149 (42%) of LVD subjects. AEs that were considered related to study drug and reported in ≥ 5% of study subjects included: headache, fatigue, and increased ALT.

A total of 134 ETV subjects and 129 LVD subjects entered off-treatment follow-up and had some safety data available for analysis. During the off-treatment period, smaller proportions of subjects in both treatment groups reported clinical AEs (43% ETV compared to 52% LVD). As in the on-treatment period analysis, no specific organ system appeared to be the target of AEs after subjects discontinued study treatment, although gastrointestinal and nervous system events were most common.

Table 10.1.1H: Patients Reporting Selected Organ System Events in Study 022 (all grade, all causality) – Off-Treatment

Organ System	ETV (N = 134)	LVD (N = 129)
Any reported AE	57 (43%)	68 (53%)
Cardiac disorders	1 (< 1%)	1 (< 1%)
Gastrointestinal disorders	18 (13%)	25 (19%)
Musculoskeletal and connective tissue disorders	7 (5%)	3 (2%)
Nervous system disorders	14 (10%)	11 (8%)
Renal and urinary disorders	3 (2%)	6 (5%)
Respiratory, thoracic and mediastinal disorders	8 (6%)	10 (7%)
Vascular disorders	1 (< 1%)	2 (2%)

Source: Medical Officer's review of the clinical datasets.

As might be expected given the smaller number of patients with data in the off-treatment period, the rates of individual AEs were much lower in this period. The most commonly reported AEs were upper abdominal pain (0 ETV, 5% LVD), pyrexia (1% ETV, 5% LVD), increased ALT (1% ETV, 10% LVD), increased AST (0 ETV, 5% LVD), and

headache (7% ETV, 6% LVD). Only 6% of ETV subjects reported an AE of Grade 3 or 4 severity and only 1% of ETV subjects had AEs that were considered related to study drug. In comparison, 13% of LVD subjects reported an AE of Grade 3 or 4 severity and 10% of subjects in this group had AEs considered related to study drug.

Serious Adverse Events

Serious AEs were reported in relatively small proportions of subjects in both treatment groups during the on treatment phase of Study 022, 27(8%) ETV subjects and 30 (8%) LVD subjects. During the on-treatment period more LVD patients experienced SAEs that were considered possibly, probably, or certainly related to study drug. Seven of the subjects had events that included elevated liver enzymes and were Grade 3 or 4 in severity. Serious AEs were less frequently reported during the off-treatment follow-up period, 2% of ETV subjects and 3% of LVD subjects.

Table 10.1.1I: Proportion of Patients Reporting Serious Adverse Events Occurring On-Treatment or Off-Treatment – Study 022

Type of Events	Entecavir (N = 354)	Lamivudine (N = 355)
All Serious AEs – On Treatment	27 (8%)	30 (8%)
SAEs possibly, probably, or certainly related to study drug	1 (<1%)	9 (3%)
SAEs Grade 3 and 4	14 (4%)	18 (5%)
SAEs Grade 3 and 4 and related to study drug	0	8 (2%)
All Serious AEs – Off Treatment	3 (2%)	4 (3%)
SAEs possibly, probably, or certainly related to study drug	0	0
SAEs Grade 3 and 4	1 (<1%)	4 (3%)
SAEs Grade 3 and 4 and related to study drug	0	0

Source: Medical Officer's review of the clinical datasets.

Serious AEs that were reported in more than one subject in either of the study arms during the on-treatment period are listed in Table 10.1.1J. Narrative summaries of SAEs were reviewed for each subject. The only SAE occurring in more than one subject during the off-treatment period was increased ALT, occurring in 2 LVD subjects.

Table 10.1.1J: Serious AEs Occurring in ≥ 2 Subjects On-Treatment – Study 022

Adverse Event (MedDRA 6.1 Preferred Term)	Entecavir (N = 354)	Lamivudine (N = 355)
Abdominal pain	2	0
ALT increased	1	5
Hepatic enzyme increased	0	2
Hepatitis B	0	2
Peritoneal hemorrhage	2	0
Pyrexia	0	2

Source: Medical Officer's review of the clinical datasets.

Deaths

There were only four deaths reported during Study 022. All subjects who died were receiving ETV during blinded study dosing. Case report forms and the applicant's narrative summaries for these patients were reviewed in detail. Each case is summarized below.

Patient #15-10127 (Argentina)
This patient was a 78 year old male with a history of mitral regurgitation and peripheral vascular disease who initiated blinded study medication (LVD) on — On — (Day 15) he was found to have peripheral edema and was started on furosemide. He was noted to have Grade 1 dyspnea beginning on — (Day 126). — (Day 192) he experienced sudden Grade 4 dyspnea, was hospitalized, and died on the same day. Additional records could not be obtained. The investigator assessed the event as not likely related to study drug but no alternative reason for death was documented.

Patient #115-10657 (Italy)
This patient was a 64 year old white male with a history of previous pacemaker implantation, right nephrectomy for renal neoplasm, and hepatomegaly who initiated blinded study medication (LVD) on — The patient had study drug interrupted from April 5, 2003, to April 13, 2003 because of an elevated lipase level. He was seen at Week 48 visit and had no problems. On — (Day 358) he was hospitalized with focal neurological deficits thought to represent a stroke. CT scans revealed cerebral, pulmonary, and bony metastases. No biopsy was performed. The patient received treatment with dexamethasone, chlorpromazine, and omeprazole and was discharged from the hospital. He died on — (Day 395). Cause of death was listed as diffuse metastasis; an autopsy was not performed. The investigator assessed the event as not related to study drug.

Paitent #136-10204 (Brazil)
This patient was a 58 year old white female with history of hypertension and myalgias who initiated blinded study medication (LVD) on —. She developed "choluria" and jaundice beginning — (Day 203) and on —, had a total bilirubin of 17.8 mg/dL (baseline 2.3), ALT of 775 U/L (baseline 141), and AST of 973 U/L (baseline 121). Study drug was interrupted on —. The patient was hospitalized on —, (Day 222) because of fatigue, hypokalemia, and increased bilirubin and INR. Repeat laboratory tests confirmed Grade 4 hyperbilirubinemia and Grade 4 elevated transaminases and she was diagnosed with Grade 4 hepatic decompensation (onset dat —). At the time of hospitalization, she was permanently discontinued from study drug. During hospitalization she also experienced Grade 4 renal insufficiency requiring dialysis, progressive hyperbilirubinemia, hypersomnia, confusion, and finally hypoxia. She was placed on mechanical ventilation on — (Day 239) but died later that day. Cause of death was listed as hepato-renal syndrome, acute hepatitis, and chronic hepatitis B infection. The investigator assessed the hyperbilirubinemia and elevated transaminases as probably related to study drug but assessed the renal insufficiency and hepatic decompensation as not related to study drug. In retrospect, this patient had log HBV DNA by PCR of 11. 2 on Day 1, 8.1 on Day 169, and 9.4 on Day 225.

Patient #209-11016 (Poland)
This patient was a 55 year old white male with a history of ischemic heart disease, hypertension, atherosclerosis, smoking, acute renal insufficiency, salmonellosis, and spondyloarthrosis who initiated blinded study medication (LVD) on —. He was last seen in clinic for a study visit on — and reported mild epigastric pain. On —, (Day 260) he complained of weakness, vomited several times, and had a headache and was taken to the local ER. Hospital records indicate that he was thought to have encephalopathy, chronic HBV, hypertension, and discopathy. He refused hospitalization and returned home. He was found dead at home later in the day. Cause of death was reported as unknown. The investigator assessed the event as not likely related to study drug.

Adverse Events Resulting in Study Drug Discontinuation

The applicant's NDA summary reports one ETV subject and 9 LVD subjects who discontinued study drug because of an AE. This reviewer identified some minor discrepancies in this reporting. Patients 125-10177 and 164-10598 are listed in the electronic dataset as discontinuing study drug because of pregnancy and alcohol abuse which are recorded as AEs, but they do not appear in the applicant's summary of discontinuations. These events were likely determined not to be true adverse events. Patient 132-10857 was reported as discontinuing study drug due to an AE in the 48-Week Study report but was determined to have Grade 3 lipase at screening and Day 1 and the reason for discontinuation was changed to "no longer met study criteria." This patient was enrolled in violation of the protocol entry criteria but received study drug and was ultimately removed from the study because of continued

elevation of his pancreatic enzymes. These subjects and their events are tabulated below.

Table 10.1.1K: Subjects Reporting Adverse Events Resulting in Study Drug Discontinuation – Study 022

Patient ID Number	Treatment	Age/Sex/Race	Days on Study Drug	Adverse Event Resulting in Discontinuation	Relationship to Study Drug
9-10978	LVD	27/M/Asian	21	Pruritic rash	Probable
13-10109	LVD	40/M/White	29	Increased ALT (Grade 4)	Possible
115-10657	LVD	64/M/White	357	Metastases to CNS (death)	Not related
125-10177	LVD	32/F/ Asian	113	Pregnancy	Not related
129-10960	LVD	41/M/Asian	30	Abnormal lipase	Possible
132-10324	LVD	56/M/White	167	Elevated lipase	Certain
136-10204	LVD	58/F/White	209	Hepatic failure, renal insufficiency	Not related
152-10242	LVD	22/M/Asian	221	Increased ALT (Grade 4)	Probable
164-10598	LVD	43/M/White	64	Alcohol abuse	Not likely
183-10574	ETV	21/M/Asian	29	Increased ALT (Grade 4)	Not likely
132-10857	LVD	50/M/White	38	Elevated amylase and lipase	Not related
185-10587	LVD	29/M/White	89	Elevated ALT and AST	Possible
40-11012	LVD	44/M/Native Hawaiian-Pacific Islander	539	Elevated ALT	Possible

Source: Medical Officer's review of the clinical datasets.

Adverse Events of Special Interest

ALT Flares

Acute exacerbations of hepatitis, sometimes called "flares," represent an important safety issue in the treatment of chronic HBV. Flares were evaluated in Study 022 for on-treatment and off-treatment follow-up periods using a standardized definition: ALT greater than 2 x baseline and 10 x ULN. Minor differences in calculating the numbers of subjects with ALT flares between the Medical Officer's review and the applicant's report can be attributed to slight differences in the method used to calculate the on-treatment and off-treatment windows.

On-treatment ALT flares were reported infrequently in Study 022 but occurred in numerically fewer subjects receiving ETV (12/354, 3%) than those receiving LVD (22/355, 6%). These flares occurred in 2 patterns. Nine of 12 ETV subjects and 11 of 22 LVD subjects experiencing flares developed increased ALT within the first 12 weeks of study treatment. These events generally coincided with decreases in HBV DNA. Three ETV and 12 LVD subjects experienced ALT flares later in treatment (one LVD subject experienced 2 flares). Among the LVD subjects in this group, ALT flare was often coincident with rebound in HBV viremia.

ALT flares led to discontinuation of blinded study treatment in one ETV subject and 3 LVD subjects. Patient #11-10185 in the LVD group experienced 2 separate flares, the first at around 8 weeks into treatment accompanied by a decrease in HBV DNA and the second at around 68 weeks into treatment accompanied by a rebound in HBV DNA. In this subject, the second ALT flare was thought to signal treatment failure and prompted discontinuation of study treatment. Most of the ALT flares were asymptomatic and not accompanied by other worrisome laboratory findings. One ETV and 2 LVD subjects experienced elevated bilirubin at the same time as an ALT flare. Only one subject developed signs and symptoms of hepatic decompensation while on treatment. Patient #136-10204 developed hepatic failure and renal insufficiency and subsequently died. For a description of this subject's clinical course, refer to the previous section on Deaths.

A total of 135 (38%) ETV subjects and 132 (37%) LVD subjects entered off-treatment follow-up. The evaluation of off-treatment flares is confounded by the fact that a relatively small proportion of subjects in either treatment arm met the criteria of Complete Response at 48 weeks and discontinued treatment (74/354 ETV and 67/355 LVD) and the remaining subjects discontinued therapy for a variety of other reasons. However, off-treatment ALT flares were relatively uncommon, occurring in one ETV subject and 8 LVD subjects. These events were all asymptomatic and none were accompanied by increases in other significant laboratory parameters. Most of these events coincided with increases in HBV DNA.

Nervous System Adverse Events

Because central nervous system toxicity was identified in pre-clinical animal studies, the occurrence of neurologic events during study treatment was reviewed in detail. We reviewed events categorized in the MedDRA System Organ Class as Nervous System disorders. Selected MedDRA Psychiatric disorders were included in the review if they were believed to overlap with potential central nervous system toxicity (eg., anxiety, anxiety disorder, insomnia, irritability, nervousness, and sleep disorder). This analysis is similar in concept to the applicant's analysis of neurologic events but includes a wider variety of events. The applicant focused their evaluation on MedDRA preferred terms that were considered to reflect events related to CNS inflammation or vasculitis.

Neurologic AEs were reported frequently during treatment in Study 022, occurring in 37% of ETV subjects and 34% of LVD subjects. Most of the reported events were graded as mild in severity and rarely resulted in study drug interruption or

discontinuation. Neurologic AEs occurred with similar frequency across treatment arms regardless of whether the events were analyzed individually or grouped. A summary of selected neurologic AEs is displayed in Table 10.1.1L.

Table 10.1.1L: Nervous System Adverse Events Reported On-Treatment – Study 022

	Study 022	
	ETV 0.5 mg (N=354)	LVD 100 mg (N=355)
Number (%) with Nervous System AEs*	131 (37%)	119 (34%)
Anxiety	7 (2%)	4 (1%)
Dizziness	29 (8%)	22 (6%)
Headache	87 (25%)	75 (21%)
Insomnia	13 (4%)	17 (5%)
Irritability	4 (1%)	1 (<1%)
Migraine	1 (<1%)	4 (1%)
Paresthesia	4 (1%)	5 (1%)
Somnolence	7 (2%)	9 (3%)
Syncope or Syncope vasovagal	3 (<1%)	2 (<1%)
Thrombotic stroke	1 (<1%)	0
Number (%) with Nervous System AEs Grades 2-4**	36 (10%)	35 (10%)

Source: Medical Officer's review of the clinical datasets.
*Includes all AEs designated as MedDRA Nervous System disorders and selected AEs designated Psychiatric disorders (anxiety, anxiety disorder, insomnia, irritability, nervousness, sleep disorder).
**Only one patient experienced a Grade 4 event (Study 022, LVD arm).

Malignancies

Because of the positive rodent carcinogenicity findings, all malignancies and pre-malignant lesions occurring during the study were evaluated. Case report forms and narrative summaries for each event were reviewed. These malignant and pre-malignant events are summarized in Table 10.1.1M.

Chronic HBV is known to increase the risk of HCC. In this study, one subject receiving ETV was diagnosed with HCC. Little is known about risk factors for other malignancy in the study population. Two of the patients reported to have malignancies were known to have had previous malignancies. Patient #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 #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.

Table 10.1.1M: Subjects Reported to have Malignancies – Study 022

Patient ID (Site#-Subject#)	Age/Sex/Race	Study Drug (Days of Exposure/Obs)	Type of Malignancy	Additional Comments
Hepatic Malignancies				
8-10672	62/M/Asian	ETV 0.5 mg (352)	Hepatocellular carcinoma	Baseline cirrhosis with Knodell Fibrosis Score=4
Non-hepatic Malignancies				
53-10168	67/M/Black	ETV 0.5 mg (480)	Prostate cancer	
80-10451	41/F/Asian	LVD 100 mg (277)	Recurrent gastric adenocarcinoma	History of gastric adenocarcinoma (pre-study)
115-10657	64/M/White	LVD 100 mg (357)	Cerebral metastases of unknown primary	History of renal cell carcinoma (pre-study)
Pre-malignant or Unclassified Lesions				
175-10643	20/F/Other	ETV 0.5 mg (242)	Breast dysplasia	

Source: Medical Officer's review of the clinical datasets.

Laboratory Findings

Evaluation of clinical laboratory parameters was conducted by analyzing the proportion of subjects in each treatment group who experienced marked laboratory abnormalities during the study. Marked laboratory abnormalities were identified using a standardized table of Recommendations for Grading Acute and Subacute Adverse Events included in the study protocol (modified from WHO recommendations). The applicant evaluated laboratory abnormalities during both on-treatment and off-treatment periods; the Medical Officer focused on findings occurring while patients were receiving study drugs. In addition to evaluating marked laboratory abnormalities, the Medical Officer also assessed mean changes from baseline for selected laboratory tests.

Among the 709 subjects who received treatment and for whom laboratory data is available, 348 (49%) were documented to have at least one laboratory abnormality ≥ Grade 3 (168 ETV, 180 LVD). As might be expected in this study population, the most commonly observed laboratory abnormalities on-treatment were those related to liver function. Most laboratory abnormalities were transient and toxicity Grades 1 and 2. Subjects experiencing ≥ Grade 3 abnormalities after baseline are summarized in Table 10.1.1N.

Table 10.1.1N: Subjects On-Treatment Experiencing ≥ Grade 3 Laboratory Abnormalities – Study 022

Laboratory Parameter	ETV 0.5 mg (N=354)	LVD 100 mg (N=355)
Absolute neutrophil count	1	1
ALT	95 (27%)	117 (33%)
Amylase	9	9
AST	33 (9%)	44 (12%)
Bicarbonate – low	1	1
Glucose – high	6	8
Glucose – low	1	1
Hemoglobin	1	0
INR	2	1
Lipase	16	15
Potassium – high	3	2
PT	4	0
Total bilirubin	8	9
Urine, blood	35	48
Urine, glucose	15	9
Urine, protein	5	7

Source: Medical Officer's review of the clinical datasets.

Mean change in selected laboratory tests for patients with paired specimens at baseline and Week 48 is shown in Table 10.1.1O. The most striking changes were seen in ALT. Laboratory evidence of liver injury is one of the key findings in chronic HBV and abnormal ALT was one of the entry criteria for the study. Treatment with either ETV or LVD resulted in a similar significant decrease in ALT over 48 weeks of dosing. Mean changes in other laboratory parameters were generally too small to be clinically meaningful.

Table 10.1.1O: Change from Baseline for Selected Laboratory Tests

Laboratory Parameter	ETV 0.5 mg (N=354)	LVD 100 mg (N=355)
ALT (IU)	N=333	N=318
Baseline	141	147
Week 48	36	45
Change from baseline	-105	-102
Creatinine (mg/dL)	N=334	N=315
Baseline	0.95	0.92
Week 48	0.96	0.95
Change	0.004	0.03

INR	N=300	N=289
Baseline	1.08	1.08
Week 48	1.04	1.04
Change	-0.04	-0.04
PT (sec)	N=287	N=270
Baseline	13.0	13.0
Week 48	12.7	12.6
Change	-0.2	-0.3
Total bilirubin (mg/dL)	N=335	N=315
Baseline	0.87	0.80
Week 48	0.83	0.81
Change	-0.04	0.01

Source: Medical Officer's review of the clinical datasets.
N=number with paired specimens at baseline and Week 48.

Additional evaluation of change in serum creatinine was performed to assess the proportion of study subjects who experienced increases in creatinine from baseline of $\geq$ 0.3 mg/dL or $\geq$ 0.5 mg/dL. The applicant calculated the number of patients in each treatment group who developed "confirmed" increases in creatinine, defined as 2 consecutive values above the analysis cut-off. They identified 30/352 (9%) ETV subjects and 32/346 (9%) LVD subjects with confirmed creatinine increase $\geq$ 0.3 mg/dL above their baseline value and 5/352 (1%) ETV and 7/346 (2%) LVD subjects with confirmed increases $\geq$ 0.5 mg/dL above their baseline. In a slightly different analysis, this reviewer assessed the number of subjects with an increase in creatinine at any time. This analysis identified 62 ETV subjects and 68 LVD subjects with any creatinine value > 0.3 mg/dL above baseline and 20 ETV and 19 LVD subjects with any creatinine value > 0.5 mg/dL above baseline.

Reviewer's Comments:
Based on pre-clinical animal studies, ETV is not expected to have significant renal toxicity. However, many patients with advanced liver disease have renal dysfunction and one of the approved treatments for chronic HBV (ADV) has known renal toxicity. The analyses of creatinine conducted for this review were similar to those conducted for the review of ADV. While the applicant's analysis of "confirmed" increase in creatinine may be indicative of more significant changes in this parameter, this Medical Officer thinks that the more inclusive analysis may also be useful. It is possible that those patients with a single significant abnormality may be subjected to additional office visits or additional laboratory assessments.

In general, the applicant's analysis of laboratory abnormalities occurring in the off-treatment period did not identify significant differences compared to the on-treatment analysis except in the analysis of ALT abnormalities. Off-treatment Grade 3 or 4 elevations of ALT were documented in 3% of ETV subjects compared to 16% of LVD subjects, a significant difference.

Conclusions

Study 022 compared treatment of chronic HBV with ETV 0.5 mg daily to standard treatment with LVD 100 mg daily over 52 weeks of randomized, blinded treatment. The study enrolled 715 adult men and women with documented e antigen positive, chronic HBV with evidence of ongoing liver inflammation as measured by biopsy and increased ALT. Prior treatment with IFN was allowed but treatment with LVD or other nucleoside analogues was prohibited. Blinded study dosing and safety monitoring continued through Week 52 at which time decisions to continue or discontinue dosing were made based on results of virologic and serologic testing conducted at Week 48. The study design allowed subjects who achieved HBV DNA by bDNA assay < LOQ and loss of e antigen to discontinue blinded treatment and continue follow-up off treatment for 24 weeks. The primary efficacy endpoint was measured by liver biopsy at Week 48 as well as a variety of virologic, serologic, biochemical, and composite secondary endpoints. The study was designed to determine non-inferiority of ETV to LVD but also planned for a second series of analyses to determine superiority of ETV if the first statistical step was passed. Very few study participants failed to receive study drug or were lost to follow-up before completing the Week 48 clinical evaluation.

For the primary efficacy endpoint, histologic improvement was defined as $\geq$ 2 point decrease in Knodell necroinflammatory score and no worsening in Knodell fibrosis score at Week 48 compared to the pre-treatment liver biopsy. Analysis of the study results confirmed that ETV was superior to LVD in achieving the primary endpoint of histologic improvement with 72% of ETV subjects and 62% of LVD subjects meeting the endpoint criteria. Sensitivity analyses conducted by both the applicant and the FDA Statistical Reviewer supported the robustness of these results. Similarly, the primary efficacy results were observed consistently across subgroups based on gender, race, age, geographic region, and a variety of other baseline disease covariates.

The study was originally designed to rely on the bDNA assay for clinical management decisions and secondary efficacy analyses. However, it became increasingly clear that the PCR assay was more sensitive over a wider range of HBV DNA levels and analyses using this assay were also included among the key secondary endpoints. Review of these secondary efficacy endpoint analyses also supported the efficacy of ETV. ETV was shown to be superior to LVD in all analyses evaluating changes in viral load regardless of the assay used to measure HBV DNA. FDA review confirmed the applicant's conclusions that ETV was superior to LVD in the proportion of subjects achieving HBV DNA < 400 copies/mL by PCR (72% vs 42%) and the mean log decrease in HBV DNA by PCR (-7.0 log vs -5.5 log). Additional secondary endpoints favoring ETV included the proportion of subjects achieving normalization of ALT (69% ETV subjects vs 61% LVD subjects). Among the secondary endpoints showing ETV equivalent to LVD were those evaluating improvement in Ishak fibrosis score (39% ETV subjects and 35% LVD subjects) and HBe seroconversion (21% ETV subjects and 18% LVD subjects).

Evaluation of the safety of ETV compared to LVD included review of data from 709 patients who received at least one dose of blinded study drug. Adverse events were extremely common in this study, occurring in 85% of subjects. In general, the pattern of clinical and laboratory AEs

documented in Study 022 were similar across treatment arms and consistent with the course of chronic HBV. The most commonly reported clinical AEs occurring on-treatment in Study 022 regardless of treatment group included upper abdominal pain, diarrhea, fever, fatigue, headache, cough, upper respiratory tract infection, and the common cold. Although AEs were reported by the majority of subjects in both treatment groups, most of the events were graded as mild or moderate in severity and the vast majority were not considered related to study drugs. Grade 3 or 4 (severe or life-threatening) AEs were reported in 49/354 (14%) ETV subjects compared to 59/354 (17%) LVD subjects and most Grade 3 or 4 events occurred in isolated cases. Grade 3 or 4 AEs occurring in more than 1% of either treatment group included: increased ALT (3% ETV, 6% LVD), increased AST (< 1% ETV, 2% LVD), and increased serum lipase (2% ETV, 1% LVD). Common AEs occurring during the off-treatment follow-up period were similar in pattern but less frequent than those observed on-treatment. Serious AEs and deaths were infrequent and observed in similar numbers across the treatment arms. Slightly more LVD subjects than ETV subjects discontinued study drug due to AEs but the numbers thought to be related to study drug were small.

Adverse events that were evaluated in more detail included nervous system or neurologic AEs, ALT flares, and malignancies. These events were of special interest based on either signals identified during animal toxicology studies (neurologic AEs and malignancies) or known complications of HBV and its treatment (ALT flares). Neurologic AEs were not identified in ETV-treated subjects significantly more frequently than in LVD-treated subjects regardless of whether the events were analyzed separately or collectively. The most common nervous system AE was headache, reported in 25% of ETV subjects and 21% of LVD subjects. In Study 022, malignancies were diagnosed in 4 subjects, 2 of whom had a history of malignancy before entering the study. To date, only a single subject in the study (receiving ETV) has been diagnosed with HCC, the most common cancer in patients with chronic HBV. ALT flares were relatively uncommon in both treatment arms, documented in 3% of subjects receiving ETV and 6% of those receiving LVD. During the off-treatment follow-up period, flares were observed in <1% of ETV subjects and 6% of LVD subjects.

Laboratory abnormalities were documented in almost all study participants over the course of the study. Abnormalities ≥ Grade 3 were identified in 49% of study subjects and were most often observed in the liver function parameters. This is to be expected since abnormal ALT was one of the study's entry criteria. Over the course of the study treatment, mean ALT decreased in both treatment groups (-105 IU in ETV subjects and -102 IU in LVD subjects). Rates of significant laboratory abnormalities (≥ Grade 3) were similar across the treatment arms.

Summary

- Study 022 supports the effectiveness of ETV in treatment of nucleoside-naïve, e antigen positive patients with chronic HBV based on the primary endpoint of improvement in liver histology over a 48 week dosing period.

- Multiple virologic, serologic, biochemical, and composite endpoints also support the efficacy of ETV compared to LVD.

- The general safety profile of ETV over at least 48 weeks of dosing is acceptable and comparable to that observed with LVD.

- Based on this study it is not possible to conclude that ETV has an adverse effect on nervous system AEs or on the development of malignancies.

- Treatment of chronic HBV with ETV may result in fewer ALT flares than treatment with LVD, although the number of these events reported in this study was small and more data are needed to make definitive conclusions.

10.1.2 AI463027: A Phase 3 study of the safety and antiviral activity of entecavir vs lamivudine in adults with chronic hepatitis B infection who are negative for hepatitis B e antigen

Protocol Study Design

AI463027 (Study 027) was a randomized, double-blind, placebo-controlled study of ETV 0.5 mg given once daily compared to LVD 100 mg given once daily in patients with confirmed chronic HBV infection who were HBeAg negative. The primary objectives of the study were to compare the proportion of patients in each treatment group who achieved histologic improvement in liver biopsy after 48 weeks of study treatment and to determine the safety profile of ETV over 52 weeks of dosing. This study was intended to use similar design, procedures, endpoints, and analysis plan as Study 022 (described in Section 10.1.1) which was conducted in e antigen positive subjects. The studies enrolled concomitantly at many of the same study sites.

Study subjects were recruited through a worldwide network of investigators in North America, South America, Europe, and Asia. Inclusion in the study required that subjects be ≥ 16 years of age (or the minimum age of consent in each country) with chronic HBV infection documented by positive HBsAg over at least 6 months and negative e antigen. Subjects were required to have evidence of chronic hepatitis by liver biopsy within 52 weeks of randomization, HBV DNA ≥ 0.7 MEq/mL by bDNA assay, serum ALT 1.3 to 10 x ULN, and compensated liver function. Subjects could have no more than 12 weeks of prior nucleoside/nucleotide therapy for HBV but could have received therapy with IFN. The last dose of any prior therapy was to be at least 24 weeks prior to randomization. Male and female patients were enrolled. Agreement to use appropriate contraception was stipulated in the protocol. Other major exclusionary criteria were concomitant HIV, HCV, or HDV, evidence of significant organ dysfunction (other than elevated transaminases), pregnancy or breastfeeding, current alcohol or drug abuse, other types of liver disease, or a screening alpha fetoprotein > 100 ng/mL. Concomitant use of medications that could cause nephrotoxicity or hepatotoxicity were not permitted during the study.

Subjects were randomized 1:1 and received blinded study drug for 52 weeks. ETV was supplied as 0.5 mg tablets. LVD was supplied as 100 mg capsules. Matching placebos were used for each of the active study components. Subjects were instructed to take their assigned study drug and placebo once daily at approximately the same time each day, preferably at bedtime. Study drugs were to be taken 2 hours before or 2 hours after food.

Study subjects were evaluated every 4 weeks during this first year of dosing and monitored for safety with a battery of clinical and laboratory assessments. Clinical AEs were recorded at each study visit throughout the study and graded according to severity using a toxicity grading system modified from the WHO guidelines. Clinical AEs were also evaluated by the investigator according to perceived relationship to blinded study drug (certainly, probably, possibly, not likely, or not related). Serious AEs and deaths were also identified and recorded. Laboratory abnormalities were also graded according to the modified WHO toxicity guidelines.

Clinical management decisions at Week 52 were based on results of virologic and biochemical studies performed at the Week 48 study visit. Responders for the Composite Endpoint (HBV DNA by bDNA assay < 3 MEq/mL and ALT < 1.25 x ULN) stopped study treatment and were followed every 4 weeks for 24 weeks off therapy to assess durability of response. Virologic-Only Responders (HBV DNA by bDNA assay < 0.7 MEq/mL but still abnormal ALT) continued blinded therapy for up to 96 weeks or until response was achieved. Study subjects continuing blinded dosing in the second year were evaluated every 8 weeks through Week 96. Virologic Non-responders (HBV DNA by bDNA $\geq$ 0.7 MEq/mL) discontinued study treatment but were eligible for the rollover study, the Early Access Program, or other available therapy.

The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved histologic improvement in their Week 48 liver biopsy. Histologic improvement was defined in the protocol as $\geq$ 2 point decrease in the Knodell necroinflammatory score and no worsening in the Knodell fibrosis score compared to the baseline biopsy. Liver biopsy results were determined by a single pathologist who was blinded to a given subject's treatment assignment and the temporal order of the biopsies.

In addition to the primary histologic endpoint, there were multiple secondary endpoints to be evaluated. These were to determine the proportion of subjects in each treatment group who achieved histologic, virologic, and composite milestones at Week 48. Among the most important of these were:

- Proportion of subjects with improvement in hepatic fibrosis from baseline to Week 48 as measured by the Ishak fibrosis score
- Reduction from baseline in covalently closed circular DNA (cccDNA)
- Proportion of subjects with HBV DNA by the bDNA assay below the LOQ
- Proportion of patients with normalization of ALT (defined as < 1.25 x ULN)
- Proportions of patients achieving Response for the Composite Endpoint
- Proportion of subjects with HBV DNA < 400 copies/mL by the PCR assay
- Refractoriness to therapy, defined as rising HBV DNA titer while on study drug after first achieving undetectable levels. Genotypic analysis was to be performed on these isolates.
- Sustained Response for the Composite Endpoint during 24 weeks off therapy follow-up
- Response for the Composite Endpoint after up to an additional 44 weeks of dosing for subjects with a Virologic-Only Response at 48 weeks
- Safety as measure by the proportion of subjects in each group who report AEs or laboratory abnormalities or who discontinue study drug due to clinical AEs or laboratory abnormalities

The applicant planned a 2-step evaluation of the efficacy endpoints. First, the non-inferiority of ETV to LVD was to be tested. If non-inferiority was established, the second step to determine superiority of ETV to LVD was to be conducted.

In addition to the primary safety endpoint noted above, common AEs, SAEs, deaths, and laboratory abnormalities were tabulated and summarized. Events of special interest such as

exacerbations in liver transaminases (ALT flares), hepatic SAEs, neurologic events, and malignancies were to be summarized.

Amendments

The original study protocol was finalized in December, 2000. Four protocol amendments were submitted after that time. Key revisions included in the amendments are summarized below.

Amendment 1 (December 7, 2001)
This amendment provided additional information regarding the findings of the animal carcinogenicity studies, the interim results of Study 014, and updated information on Studies 005 and 007. It provided for the collection of blood for HBV genotype at baseline and Week 48 and described assessment of response at Week 48 according to HBV subtype. Entry criteria were modified slightly to allow greater enrollment. The amendment also added additional measurements of HBV DNA by bDNA and by PCR.

Amendment 2 (April 8, 2002)
This amendment further broadened the entry criteria by decreasing the allowed entry HBV DNA by bDNA to $\geq$ 0.7 MEq/mL and decreased the required level of prior HBV viremia by PCR to > 1 x 105 copies/mL. Additional measurements of HBV DNA by PCR were included.

Amendment 3 (January 26, 2003)
Amendment 3 modified several important study procedures. It stated that subjects who discontinued study therapy before Week 48 should have all Week 48 procedures performed at the time of discontinuation including the recommended liver biopsy. It also specified that all subjects who discontinued study drug (not just Responders for the Composite Endpoint) be followed off treatment every 4 weeks for 24 weeks. A secondary endpoint of improvement in hepatic fibrosis score measured by the Ishak scoring system was added. The secondary endpoint of refractoriness to therapy was deleted and replaced with an endpoint for Virologic Rebound, defined as $\geq$ 1 log increase in HBV DNA by bDNA from the nadir on treatment. Patients who required additional therapy for HBV after participating in the study would be allowed to enroll in the open-label rollover protocol or the open-label ETV Early Access Program.

Amendment 4 (January 9, 2004)
Amendment 4 was submitted in response to the growing awareness that some patients receiving treatment for chronic HBV or those discontinuing active treatment were at risk for ALT flares and severe hepatic AEs. This amendment required that investigators report ALT flares (defined as ALT > 2 x baseline and > 10 x ULN) with or without other accompanying laboratory abnormalities and any events suggestive of hepatic decompensation as SAE under the expedited reporting guidelines. The Dose Modifications section of the protocol was revised to provide investigators with increased flexibility to continue study drugs in the face of increased ALT/AST. Treatment management for Virologic-Only Responders who experienced rebound of HBV DNA by bDNA assay during the second year of dosing (loss of response) was clarified to indicate that investigators could initiate alternative treatment or enroll the subject in the rollover or compassionate access program for ETV.

Post Hoc Changes

No significant post hoc changes in the study analyses were noted.

Study Results

Disposition

A total of 1468 subjects were screened for Study 027 from 30 countries. Of these, 648 subjects were randomized to receive study drug. There were 820 subjects screened but never randomized and who received no study drug. Of these, 774 were described as failing screening because they "no longer met study criteria," 35 subjects "withdrew consent," 6 were "lost to follow-up," 2 were not randomized because of "non-compliance," and 1 subject each was not randomized because of "adverse event," "pregnancy," or "randomization closed."

Of the 648 subjects randomized, 638 received at least one dose of blinded study drug. Table 10.1.2A summarizes the disposition of study subjects after randomization through the study data cut-off of September 10, 2004. Similar proportions of ETV-treated subjects and LVD-treated subjects received study drug, completed the first year of dosing, and continued to the second year of dosing. The applicant noted that "treatment failure/lack of efficacy" as a reason for discontinuation from study was based on the investigators clinical assessment, not the protocol-defined efficacy endpoints.

Table 10.1.2A: Disposition of Subjects - Study 027

Disposition of Subjects	ETV	LVD
All randomized	331	317
Never dosed	6 (2%)	4 (1%)
Received study drug	325 (98%)	313 (99%)
Did not complete first year of dosing	14 (4%)	17 (5%)
Adverse event	6	9
Death	2	0
Lost to follow-up	0	2
Noncompliance	2	2
Subject withdrew consent	4	4
Completed first year of dosing	311 (94%)	296 (93%)
Continued to second year of dosing	46 (14%)	59 (19%)

Did not complete second year of dosing	7 (2%)	12 (4%)
Lost to follow-up	1	1
Non compliance	2	0
Subject no longer meets study criteria	4	2
Treatment failure/lack of efficacy	0	9
Completed second year of dosing	31 (9%)	37 (12%)

Source: AI463027: Clinical Study Report Addendum 01, Tables 8.1A, pages 68.

Of those who received study drug, a greater proportion of ETV subjects than LVD subjects entered the 24-week follow-up phase (92% vs 84%). The criteria for Response and discontinuing treatment after 48 weeks included HBV DNA by bDNA assay < 0.7 MEq/mL and ALT < 1.25 x ULN. Disposition of subjects entering follow-up is summarized in Table 10.1.2B. More LVD subjects discontinued follow-up before 24 weeks and 91% of LVD subject discontinuations in this phase were because of investigator assessment of treatment failure or lack of efficacy. Conversely, more ETV subjects completed the 24-week follow-up phase of the study although 69% of ETV subject discontinuations were also due to treatment failure.

Table 10.1.2B: Disposition of Subjects Entering 24-Week Follow-up – Study 027

Disposition of Subjects	ETV	LVD
Received study drug	325	313
Entered 24-week follow-up	299 (92%)	263 (84%)
Discontinued 24-week follow-up	42 (13%)	105 (34%)
Adverse event	0	1
Lost to follow-up	8	2
Non-compliance	0	3
Subject no longer meets study criteria	1	0
Subject withdrew consent	4	3
Treatment failure/lack of efficacy	29	96
Completed 24-week follow-up	235 (72%)	148 (47%)

Source: AI463027: Clinical Study Report Addendum 01, Table 8.1B, page 72.

Demographics and Baseline Characteristics

Patients were recruited from 121 study sites (each enrolling 1 to 28 subjects) representing the global population with chronic HBV. Of the 648 randomized subjects, 37 were from the

U.S. Treatment groups were similar in demographic profile and baseline HBV disease characteristics as shown in Tables 10.1.2C and 10.1.2D. The subjects enrolled in Study 027 entered the study with a variety of HBV subtypes the most common of which were subtype A (33 ETV, 34 LVD), subtype B (46 ETV, 62 LVD), subtype C (61 ETV, 53 LVD), and subtype D (157 ETV, 135 LVD). These 4 subtypes accounted for about 80% of subject's HBV isolates.

Table 10.1.2C: Demographic Data – Study 027

Demographic Characteristic	ETV	LVD	Total
All randomized	331	317	648
Male/Female (%)	76%/24%	75%/25%	76%/24%
Mean age in years (range)	44.3 (18-76)	44.5 (18-77)	44.4 (18-77)
Race			
Asian	123 (37%)	130 (41%)	253 (39%)
Black/African American	8 (2%)	7 (2%)	15 (2%)
Native Hawaiian/Pacific Islander	1 (<1%)	0	1 (<1%)
White	199 (60%)	180 (57%)	379 (58%)
(Ethnicity: Hispanic)	(1/<1%)	(1/<1%)	(2/<1%)
Geographic region			
Asia	107 (32%)	105 (33%)	212 (33%)
Europe	161 (49%)	151 (48%)	312 (48%)
North America	28 (8%)	27 (9%)	55 (8%)
South America	35 (11%)	34 (11%)	69 (11%)

Source: Medical Officer's review of the clinical datasets.

Table 10.1.2D: Baseline Disease Characteristics – Study 027

Baseline Disease Characteristic mean (median)	ETV (N = 331 randomized, N = 303 with histology)	Lamivudine (N = 317 radomized, N = 293 with histology)
ALT (IU)	141 (106)	143 (105)
AST (IU)	79 (60)	79 (61)
Total bilirubin (mg/dL)	0.9 (0.8)	0.8 (0.7)
Prothrombin time (sec)	13.2 (12.9)	12.9 (12.3)
INR	1.1 (1.1)	1.1 (1.1)
HBV DNA by bDNA assay (MEq/mL)	173 (27)	206 (20)
HBV DNA by PCR assay (copies/mL)	8.8E+10 (3.5E+7)	7.0E+10 (3.3E+7)
Log10 PCR	7.7 (7.5)	7.6 (7.5)

Knodell necroinflammatory score	8.0 (9.0)	7.7 (8.0)
Knodell fibrosis score	1.9 (1.0)	1.9 (1.0)
Ishak fibrosis score	2.4 (2.0)	2.5 (2.0)

Source: Medical Officer's review of the clinical datasets.

Efficacy

For a complete review of the primary efficacy analysis and selected secondary analyses, please see the Statistical Review conducted by Dr. Tom Hammerstrom. The discussion of efficacy included below is derived from his analyses, additional calculations performed by the Medical Officer, and the applicant's stated results as reported in the AI463027 Clinical Study Report submitted in the initial NDA material and the Clinical Study Report Addendum 01 that was submitted as part of the safety update later in the review cycle.

Primary

The primary efficacy endpoint for Study 027 was histologic improvement in the Week 48 liver biopsy compared to the baseline biopsy. Histologic improvement was defined as $\geq$ 2 point improvement in Knodell necroinflammatory score and no worsening in the Knodell fibrosis score. The applicant used as their primary analysis a modified ITT analysis that evaluated only subjects who had an adequate baseline biopsy with a Knodell necroinflammatory score ≥ 2 and counted subjects with a missing or inadequate Week 48 biopsy as treatment failures. Results of this analysis were confirmed by Dr. Hammerstrom during his statistical review of efficacy (see his review for detailed discussion).

Among the 638 subjects who received study drug, 623 (98%) had a baseline biopsy performed and 569 (89%) had a Week 48 biopsy sample. Not all of the biopsy samples at baseline or at Week 48 sampling were adequate for evaluation. Of the 583 subjects who had an evaluable baseline biopsy (adequate sample and a necroinflammatory score > 2), 515 also had an adequate Week 48 sample and were fully evaluable for histologic endpoints. This number represents 88% of the subjects with baseline biopsies but 81% of the treated study population. Overall, the applicant achieved an acceptable rate of biopsies to evaluate the primary endpoint.

In the applicant's analysis of the primary endpoint, ETV was superior to LVD in the proportion of subjects achieving overall histologic improvement. In this study the number of missing and inadequate Week 48 biopsies was similar across the two treatment groups. The applicant performed additional analyses using different methods to calculate efficacy including a more conservative analysis using a non-completer = failure method with all randomized patients. This method counts all patients with missing or inadequate biopsy data at either baseline or Week 48 as treatment failures. This sensitivity analysis again showed that ETV was superior to LVD in achieving the primary endpoint of

histologic improvement. These results are summarized in Table 10.1.2E below. FDA statistical review confirmed these analyses and conducted additional sensitivity analyses supporting the primary efficacy conclusions.

Table 10.1.2E: Histologic Improvement at Week 48 – Study 027

	Entecavir (N = 331 randomized)	Lamivudine (N = 317 randomized)
Primary endpoint analysis (using evaluable baseline biopsy)	N=296	N=287
Histologic improvement	208 (70%)	174 (61%)
No improvement	57 (19%)	76 (26%)
Inadequate biopsy Week 48	7 (2%)	4 (1%)
Missing biopsy Week 48	24 (8%)	33 (11%)
Proportion with improvement: Difference estimate (95% CI)	9.6 (2.0, 17.3) p = 0.014	
Sensitivity analysis (using all randomized subjects)		
Histologic improvement*	210 (63%)	174 (55%)
No improvement	62 (19%)	80 (25%)
Inadequate baseline biopsy	12 (4%)	15 (5%)
Missing baseline biopsy	14 (4%)	8 (3%)
Inadequate Week 48 biopsy	7 (2%)	4 (1%)
Missing Week 48 biopsy	26 (8%)	36 (11%)
Proportion with improvement: Difference estimate (95% CI)	8.6 (1.0, 16.1) p = 0.027	

Source: AI463027: Clinical Study Report, Table 10.1.1A, page 153 and Table 10.1.1D, page 157.
*Includes improvement for subjects with baseline Knodell necroinflammatory score of 1 or 0 if Week 48 necroinflammatory score of 0 and no worsening of Knodell fibrosis.

The applicant conducted subgroup analyses of the primary endpoint according to multiple demographic and baseline disease characteristics. Each of these analyses was performed using their primary efficacy analysis methodology (modified ITT, non-completer = failure, patients with evaluable baseline biopsy). In the subgroup analyses by region, ETV maintained at least numerical superiority over LVD in Europe, Asia, and South America. Among the small group of subjects enrolled in North America, the proportion of subjects achieving the primary endpoint was numerically greater among LVD subjects (19/25, 76%) than ETV subjects (14/23, 61%) but this was not statistically significant. Among subgroups identified by possible HBV prognostic factors ETV appeared to be superior to LVD: in subjects with ALT $\geq$ 2.6 x ULN, in male subjects, in non-Asian subjects, in subjects with HBV subtype D, and in those with no prior IFN use. In other subgroups (ALT < 2.6 x ULN, female, Asian, HBV subtype, prior IFN use), ETV was non-inferior to LVD. Dr. Hammerstrom confirmed results of these subgroup analyses and concluded that ETV was non-inferior to LVD in all subgroups evaluated and statistically superior in many subgroups.

Secondary

The applicant conducted multiple secondary analyses of efficacy using histologic, virologic, and composite endpoints. The analyses of these endpoints used a similar modified ITT method with non-completer = failure based on patients with available baseline data. Some of these analyses are summarized in Table 10.1.2F below. In general, these results were confirmed by Dr. Hammerstrom in his statistical review and/or this Medical Officer although not all of the applicant's secondary analyses were duplicated during the review process.

One of the additional histologic endpoints evaluated as a secondary endpoint was improvement in the Ishak fibrosis score, another well-accepted method of grading liver histology. In the analysis of this histologic endpoint, the proportions of subjects with improvement were similar in the ETV and LVD groups. Another of the hepatic markers of HBV infection, covalently closed circular DNA (cccDNA) was evaluated from the subset of subjects who had their baseline biopsies at the time of screening. This marker is considered an indicator of actively replicating HBV in hepatocytes and its clearance is thought to be necessary for long-term elimination of the virus. The mean change from baseline in cccDNA from baseline to Week 48 was similar in the two treatment groups.

The secondary analyses verify that ETV provides superior virologic suppression of HBV compared to LVD at 48 weeks of study dosing as measured by either the HBV DNA bDNA assay or the HBV DNA PCR assay. Subjects receiving ETV experienced a greater decrease in mean HBV DNA by PCR than did those receiving LVD. Similarly, while the majority of subjects in both treatment groups achieved normalization of ALT over 48 weeks, the subjects receiving ETV achieved this endpoint slightly more frequently.

In Study 027, the protocol-defined criteria for Composite Response (HBV bDNA < 0.7 MEq/mL and ALT < 1.25 x ULN) was achieved by a majority of subjects in both treatment groups. More ETV-treated subjects achieved this clinical management endpoint than did LVD-treated subjects (85% vs 78%). A relatively small number of subjects in both groups were Virologic-only Responders and eligible for continuation into the second year of blinded dosing according to the protocol. About 5% of subjects in each group had missing Week 48 data and could not be categorized.

Table 10.1.2F: Secondary Efficacy Endpoints at Week 48 – Study 027

	ETV (N = 325 treated)	LVD (N = 313 treated)
Improvement Ishak fibrosis score (≥ 1 point decrease)	36%	38%
Hepatic cccDNA (mean change from baseline)	-0.5 log copies/HGEq (N = 107)	-0.5 log copies/HGEq (N = 104)

HBV DNA by bDNA < LOQ (< 0.7 MEq/mL)	95%*	89%
HBV DNA by PCR < LOQ (< 400 copies/mL)	91%*	73%
Log HBV DNA by PCR (mean change from baseline)	-5.2*	-4.7
Protocol-defined ALT normalization (< 1.25 x ULN)	86%	81%
Composite Response (HBV bDNA < LOQ and ALT < 1.25 x ULN)	85%*	78%
Virologic-only Response (HBV bDNA < LOQ, ALT abnormal ≥ 1.25 x ULN)	10%	11%
Non-Responders (HBV bDNA > LOQ)	<1%	6%

Source: AI463027 Clinical Study Report and AI463027 Clinical Study Report Addendum 01.
#Hepatic cccDNA analysis required biopsy at time of screening. Retrieval of archived biopsies, allowed for enrollment, not adequate for testing.
*Statistically significant difference between ETV and LVD favoring ETV.

Reviewer's Comments
The applicant chose their cut-off for normalization of ALT based on use of laboratory toxicity grading tables that set Grade 1 ALT toxicity at > 1.25 x ULN. The Review Team disagreed with this choice of ALT normalization and believed that true normalization of ALT should be calculated as < 1.0 x ULN. Our calculations of ALT normalization using the stricter criteria identified 76% of ETV subjects compared to 68% of LVD subjects achieving the endpoint. This more conservative calculation favored ETV.

At the time of the original NDA submission, data were insufficient to assess the durability of the Composite Response in Study 027. An analysis of sustained response was included in the AI463027 Clinical Study Addendum 01 submitted with the NDA safety update during the review cycle. Of the 275 ETV subjects and 245 LVD subjects who met the Composite Response criteria, 259 ETV subjects and 220 LVD subjects discontinued blinded study treatment per protocol and were followed off-treatment. Forty-seven subjects who were eligible to discontinue treatment based on Composite Response at Week 48 continued blinded study drug in the second year of dosing. These protocol deviations were balanced across the two treatment arms and were unlikely to impact results of the analysis of sustained response.

The applicant evaluated the cohort of subjects who discontinued blinded study treatment and were followed off-treatment to assess the durability of the Composite Response. In this cohort, only 124/259 (48%) ETV subjects compared to 78/220 (35%) LVD subjects maintained the Composite Response criteria through 24 weeks of off-treatment follow-up. An exploratory analysis of the Composite Response cohort identified that 96% of ETV subjects and 85% of LVD subjects achieved HBV DNA by PCR < 400 copies/mL

at the end of study dosing. At the end of off-treatment follow-up, only 4% of ETV subjects and 3% of LVD subjects maintained this level of HBV DNA by PCR.

Reviewer's Comments:
The results of this analysis add to the accumulating evidence that e antigen negative patients being treated for chronic hepatitis B should not discontinue treatment based on HBV DNA levels or ALT improvements. Although the majority of subjects in both arms met the protocol defined Composite Response and most met the stricter criteria of HBV DNA by PCR < 400 copies/mL, very few of those discontinuing treatment sustained suppression of HBV replication over 24 weeks.

Safety

The applicant evaluated the safety of ETV compared to LVD in Study 027 by assessing clinical and laboratory events in all patients who received at least one dose of blinded study drug: 325 ETV subjects and 313 LVD subjects. They divided the safety analysis into three periods. The on-treatment period includes all data from patients treated through the data cut-off (September 10, 2004). The off-treatment follow-up includes data from the 560 patients who discontinued blinded study treatment for any reason and had safety data while not receiving other HBV therapy. The 24-week follow-up includes all safety data collected after subjects discontinued blinded treatment regardless of whether they received other HBV therapy (excluding those enrolled in the BMS rollover protocol). As there were only 2 additional subjects in the 24-week follow-up compared to the off-treatment follow-up cohort, the FDA safety analysis included only the on-treatment and off-treatment follow-up periods.

Adverse Events

The applicant tabulated clinical AEs using preferred terms and system organ class designations as listed in MedDRA 7. In general, the Clinical Reviewer's analyses confirmed the applicant's summary of AEs reported during Study 027 in both on-treatment and off-treatment periods. Very minor discrepancies in rates of AEs could be attributed to slightly different methods of calculating the on-treatment period for each subject.

Clinical AEs were reported frequently in this population of subjects with serious underlying illness. Combined non-serious and serious AEs were reported in 76% of ETV subjects and 80% of LVD subjects while on study treatment. These AE's were reported in a wide variety of organ systems as noted in Table 10.1.2G. Events categorized by organ system were similar between the two treatment groups. Nervous system toxicity was identified in the pre-clinical animal toxicology studies. In this study, numerically slightly fewer subjects receiving ETV reported nervous system AEs compared to those receiving LVD. These events will be evaluated in more detail later in the review (see Events of Special Interest).

Table 10.1.2G: Patients Reporting Selected Organ System Events in Study 027 (all grade, all causality) – On-Treatment

Organ System	Entecavir (N = 325)	Lamivudine (N = 313)
Cardiac disorders	4 (1%)	6 (2%)
Gastrointestinal disorders	111 (34%)	98 (31%)
Hepatobiliary disorders	10 (3%)	3 (<1%)
Musculoskeletal and connective tissue disorders	65 (20%)	64 (20%)
Neoplasms benign, malignant, and unspecified	7 (2%)	4 (1%)
Nervous system disorders	82 (25%)	85 (27%)
Psychiatric disorders	40 (12%)	33 (11%)
Renal and urinary disorders	23 (7%)	17 (5%)
Respiratory, thoracic and mediastinal disorders	48 (15%)	51 (16%)
Skin and subcutaneous tissue disorders	36 (11%)	40 (13%)
Vascular disorders	11 (3%)	17 (5%)

Source: Medical Officer's review of the clinical datasets.

The most common AEs reported while on-treatment in Study 027, regardless of treatment group, were headache, upper respiratory infection, upper abdominal pain, fatigue, influenza, and nasopharyngitis (preferred term for "common cold"). AEs reported in at least 5% of either treatment group are summarized in Table 10.1.2H. The AEs arthralgia, blood amylase increased, and influenza were reported slightly more frequently among ETV-treated subjects but none of the differences in AEs were significant across the treatment groups.

Table 10.1.2H: Adverse Events Reported in ≥ 5% of Patients On-Treatment in Study 027 (all grades, all causality)

Adverse Event (MedDRA 7 Preferred Term)	ETV (N = 325)	LVD (N = 313)
All patients with AE	246 (76%)	249 (80%)
Abdominal pain	12 (4%)	16 (5%)
Abdominal pain upper	30 (9%)	24 (8%)
Arthralgia	25 (8%)	15 (5%)
Back pain	26 (8%)	25 (8%)
Blood amylase increased	16 (5%)	7 (2%)
Cough	20 (6%)	20 (6%)
Diarrhea	20 (6%)	12 (4%)

Dizziness	13 (4%)	17 (5%)
Dyspepsia	26 (8%)	19 (6%)
Fatigue	27 (8%)	27 (9%)
Headache	50 (15%)	53 (17%)
Influenza	29 (9%)	18 (6%)
Insomnia	17 (5%)	19 (6%)
Myalgia	16 (5%)	12 (4%)
Nasopharyngitis	28 (9%)	24 (8%)
Nausea	17 (5%)	12 (4%)
Pyrexia	14 (4%)	16 (5%)
Upper respiratory tract infection	44 (14%)	45 (14%)

Source: Medical Officer's review of the clinical datasets.

Most of the AEs reported on-treatment by subjects in both treatment groups were mild or moderate in severity. Grade 3 or 4 (severe or life-threatening) AEs were reported in 27/325 (8%) ETV subjects compared to 37/313 (12%) LVD subjects. Most of the Grade 3 or 4 events occurred as isolated cases. Grade 3 or 4 AEs occurring in more than 1% of either treatment group included: increased lipase (2% ETV, 2% LVD) and increased ALT (<1% ETV, 3% LVD).

Similarly, most of the AEs reported on-treatment in both treatment groups were considered by the investigators not to be related to study drug administration. Among subjects receiving ETV, 109 (34%) reported an AE considered possibly, probably, or certainly related to study drug. Among subjects receiving LVD, 102 (33%) reported an AE considered related to study drug. Events considered related to study drug occurring in at least 3% of subjects in either treatment arm included: headache (6% ETV, 7% LVD), increased lipase (4% ETV, 4% LVD), increased amylase (4% ETV, 2% LVD), dizziness (3% ETV, 4% LVD), fatigue (3% ETV, 4% LVD), nausea (3% ETV, 3% LVD), and abdominal pain (3% ETV, 2% LVD).

A total of 297 ETV subjects and 263 LVD subjects entered off-treatment follow-up and had some safety data available for analysis. During the off-treatment period, smaller proportions of subject in both treatment groups reported clinical AEs (51% ETV subjects, 55% LVD subjects). Off-treatment AEs involved a variety of organ systems as shown in Table 10.1.2I.

Table 10.1.2I: Patients Reporting Selected Organ System Events Off-Treatment in Study 027 (all grade, all causality)

Organ System	Entecavir (N = 297)	Lamivudine (N = 263)
Cardiac disorders	1 (<1%)	0
Gastrointestinal disorders	32 (11%)	22 (8%)
Hepatobiliary disorders	7 (2%)	4 (2%)

Musculoskeletal and connective tissue disorders	23 (8%)	22 (8%)
Neoplasms benign, malignant, and unspecified	1 (<1%)	1 (<1%)
Nervous system disorders	23 (8%)	19 (7%)
Psychiatric disorders	7 (2%)	5 (2%)
Renal and urinary disorders	9 (3%)	8 (3%)
Respiratory, thoracic and mediastinal disorders	10 (3%)	14 (5%)
Skin and subcutaneous tissue disorders	11 (4%)	10 (4%)
Vascular disorders	4 (1%)	3 (1%)

Source: Medical Officer's review of the clinical datasets.

Specific AEs were also reported in smaller numbers of subjects. AEs reported in at least 5% of subjects in either treatment group during the off-treatment follow-up period are displayed in Table 10.1.2J. During this phase of the study ALT and AST increases reported as AEs occurred more often in the LVD group. Fatigue was also reported in a slightly higher proportion of subjects in the LVD group.

Table 10.1.2J: Adverse Events Reported in ≥ 5% of Patients Off-Treatment in Study 027 (all grades, all causality)

Adverse Event (MedDRA 7 Preferred Term)	ETV (N = 297)	LVD (N = 263)
All patients with AE	151 (51%)	144 (55%)
ALT increased	20 (7%)	39 (15%)
AST increased	8 (3%)	17 (6%)
Fatigue	4 (1%)	13 (5%)
Headache	14 (5%)	14 (5%)
Nasopharyngitis	14 (5%)	10 (4%)
Upper respiratory tract infection	14 (5%)	10 (4%)

Source: Medical Officer's review of the clinical datasets.

Most of the off-treatment AEs were mild or moderate in severity. Grade 3 or 4 events were reported in 17/297 (6%) ETV subjects and 25/263 (10%) LVD subjects during their off-treatment follow-up. AEs considered by the investigators to be possibly, probably, or certainly related to previous study drug were reported in 15 ETV subjects (5%) and 11 LVD subjects (4%).

Serious Adverse Events

Serious AEs were reported in small proportions of subjects in both treatment groups during the on-treatment phase of Study 027, 21 (6%) ETV subjects and 24 (8%) LVD subjects. Only 2 LVD subjects experienced SAEs that were considered possibly or probably related to study drug administration, one with elevated lipase and one with atrioventricular block. Most of the reported SAEs were mild or moderate in severity. Grade 3 or 4 SAEs occurred in 9 (3%) ETV subjects and 13 (4%) LVD subjects. Serious AEs reported in more than one subject on-treatment in either treatment group are displayed in Table 10.1.2K.

Table 10.1.2K: Serious AEs Occurring in ≥ 2 Subjects On-Treatment – Study 027

Adverse Event (MedDRA 7 Preferred Term)	Entecavir (N = 325)	Lamivudine (N = 313)
Abdominal pain (NOS or upper)	1	2
Benign prostatic hypertrophy	0	2
Breast cancer	1	1
Chest pain	1	1
Diabetes	0	1
Hepatic neoplasm malignant	2	2
Kidney stone	2	0
Post-procedural pain	1	2
Pyrexia	0	2
Traffic accident	2	0
Urinary tract infection	1	1

Source: Medical Officer's review of the clinical datasets.

Serious AEs were reported slightly less frequently during the off-treatment follow-up period, 15 (5%) ETV subjects and 18 (7%) LVD subjects. Off-treatment SAEs reported in more than one subject included: increased ALT (8 ETV, 9 LVD), increased AST (3 ETV, 1 LVD), hepatitis (1 ETV, 2 LVD), intervertebral disc protrusion (2 LVD), and increased transaminases (2 LVD). Two subjects in each arm experienced SAEs that were considered possibly or probably related to study drug and all were hepatic events. The 2 ETV subjects were described as having increased ALT and relapsed hepatitis B. The 2 LVD subjects were described as having acute exacerbation of hepatitis and hepatocellular carcinoma.

Deaths

Only 2 deaths were reported during Study 027, both in subjects receiving ETV. Both deaths occurred during the first phase of dosing (first 52 weeks).

Subject #12-51342
This subject was a 53 year old Asian female with a history of hypertension, abdominal pain, and cirrhosis who initiated blinded study medication (ETV) of — .. On — (Day 257) she developed elevated ALT of 70, AST of 115 U/L, and total bilirubin of 2.3 mg/dL. An ultrasound performed on — (Day 288) revealed a diffuse infiltrative process in the liver and a follow-up CT scan confirmed a markedly enlarged liver with multinodular heterogenous infiltrative process with occlusion of the portal venous system. She was admitted to the hospital on — (Day 291) and had fine needle biopsy of the liver that confirmed hepatocellular carcinoma. She was treated with cisplatin. She was readmitted to the hospital or — (Day 314) because of vomiting, diarrhea, dehydration, tachypnea, electrolyte abnormalities, and markedly abnormal liver function tests and died later that day. Study drug was continued at least through — , her Week 44 study visit. The cause of death was reported as end stage liver disease secondary to hepatocellular carcinoma. The investigator assessed the event as not related to study drug.

Subject #189-50838
This subject was a 61 year old white male with a medical history of chronic cholecystitis, diabetes mellitus, and hepatomegaly who initiated blinded study medication (ETV) on — . He was hospitalized on — 2 because of abdominal pain, fever, weakness, and headache. Chest X-ray revealed bilateral pneumonia and right hydrothorax. After initial improvement with antibiotics, his condition deteriorated on — with worsening diabetes, fever, headache, and abdominal pain. Study drug was discontinued on — (Day 53). He developed anuria and ketosis, became comatose, and died on — (Day 54). Cause of death was reported as multi-organ failure (acute renal failure, acute liver failure, acute cardiac insufficiency, pneumonia, and decompensated diabetes). The investigator assessed the events as not related to study drug.

Adverse Events Resulting in Study Drug Discontinuation

Fifteen subjects discontinued blinded study drug because of AEs, 6 (2%) receiving ETV and 9 (3%) receiving LVD. Eight of these events (4 ETV, 4 LVD) were considered possibly or probably related to study drug. These subjects and the pertinent events are tabulated below.

Table 10.1.2L: Subjects Reporting Adverse Events Resulting in Study Drug Discontinuation – Study 027

Patient ID Number	Treatment	Age/Sex/Race	Days on Study Drug	Adverse Event Resulting in Discontinuation	Relationship to Study Drug
101-50558	ETV	46/M/White	309	Hepatocellular carcinoma	Not likely
112-50503	ETV	38/F/White	59	Upper abdominal pain, increased lipase and	Possibly

				amylase	
115-50663	ETV	37/M/White	337	Increased lipase and amylase	Probably
12-50850	LVD	63/M/Asian	38	Chest pain, right lower abdominal pain, nerve compression, fatigue	Not related
121-50122	LVD	38/M/Asian	141	Increased ALT	Probably
144-50119	LVD	55/F/White	5	Dizziness, headache, flatulence	Possibly
153-51276	ETV	43/M/White	141	Increased amylase and lipase	Probably
155-50162	LVD	50/M/White	40	Exacerbation of chronic pancreatitis	Not likely
193-50490	LVD	66/F/White	357	Carcinoma in situ (breast)	Not likely
206-51097	LVD	37/M/White	283	Increased lipase	Probably
3-50963	LVD	20/M/Asian	68	Depression, suicidal ideation	Not likely
3-50976	ETV	50/F/Asian	75	Psoriasis	Possibly
40-50662	LVD	42/M/Asian	40	Hepatocellular carcinoma (transplanted)	Not related
5-50742	ETV	72/M/Asian	322	Gastric adenocarcinoma	Not related
94-50186	LVD	46/M/White	29	Increased ALT and AST	Possibly

Source: Medical Officer's review of the clinical datasets.

Events of Special Interest

ALT Flares

Acute exacerbations of hepatitis, or ALT flares, were evaluated in Study 027 for on-treatment and off-treatment follow-up periods using a standardized definition: ALT greater than 2 x baseline and 10 x ULN. Minor differences in calculating the numbers of subjects with ALT flares between the Medical Officer's review and the applicant's report can be attributed to slight differences in the method used to calculate the on-treatment and off-treatment windows.

ALT flares occurred very infrequently during the on-treatment phase of Study 027. On-treatment ALT flares were documented in 3 ETV subjects and 5 LVD subjects (one of whom had 2 flares). Two ETV subjects and 2 LVD subjects experienced ALT flares within the first 12 weeks of dosing, and were preceded or accompanied by decreases in HBV DNA. One ETV subject and 4 LVD subjects experienced ALT flares that occurred later in dosing and were accompanied by increasing HBV DNA levels. One LVD subject had a flare associated with ascites. All other on-treatment ALT flares were asymptomatic. No subjects discontinued study drug because of an ALT flare, although one subject was identified as having a flare one day after discontinuing ETV at study endpoint.

As noted in the discussion of efficacy, a majority of patients in both arms of Study 027 met the protocol criteria of Composite Response, discontinued study treatment, and were followed off-treatment. A total of 297 ETV subjects and 263 LVD subjects had some follow-up off-treatment. ALT flares were comparable but more common in both treatment groups during the off-treatment follow-up period than during treatment, occurring in 23 (8%) ETV subjects and 29 (11%) LVD subjects. All subjects who experienced an off-treatment ALT flare had HBV DNA by bDNA below the LOQ at the time of discontinuing study drug. About 80% of the off-treatment flares in both treatment groups were preceded or accompanied by documented increases in HBV DNA by bDNA. None of the ETV subjects experiencing ALT flare had signs or symptoms of worsening liver disease. One of the LVD subjects experienced a flare that was accompanied by a clinically significant increase in PT. The applicant calculated that the median time to flare was 23.9 weeks for the ETV subjects and 9.4 weeks for the LVD subjects.

Nervous System Adverse Events

Because central nervous system toxicity was identified in pre-clinical animal studies, the occurrence of neurologic events during study treatment was reviewed in detail. We reviewed events categorized in the MedDRA System Organ Class as Nervous System disorders. Selected MedDRA Psychiatric disorders were included in the review if they were believed to overlap with potential central nervous system toxicity (eg., anxiety, anxiety disorder, insomnia, irritability, nervousness, and sleep disorder). This analysis is similar in concept to the applicant's analysis of neurologic events but includes a wider variety of events. The applicant focused their evaluation on MedDRA preferred terms that were considered to reflect events related to CNS inflammation or vasculitis.

In both the applicant's analysis and the FDA analysis, neurologic AEs occurred with similar frequency across treatment arms regardless of whether the events were analyzed individually or grouped. These events were common and occurred in about 30% of study subjects in the FDA analysis. Most of the reported events were graded as mild in severity and rarely resulted in study drug interruption or discontinuation. A summary of selected neurologic AEs is displayed in Table 10.1.2M.

Table 10.1.2M: Summary of Nervous System Adverse Events – Study 027

	ETV (N=325)	LVD (N=313)
Number with Nervous System AEs*	96 (30%)	98 (31%)
Anxiety	5 (2%)	2 (<1%)
Dizziness	13 (4%)	17 (5%)
Headache	50 (15%)	53 (17%)
Insomnia	17 (5%)	19 (6%)
Irritability	0	2 (<1%)

Lethargy	3 (<1%)	4 (1%)
Migraine	4 (1%)	1 (<1%)
Paresthesia	5 (2%)	5 (2%)
Somnolence	3 (<1%)	3 (<1%)
Syncope or Syncope vasovagal	1 (<1%)	1 (<1%)
Thrombotic stroke	0	0
Number with Nervous System AEs Grades 2-4**	26 (8%)	23 (7%)

*Includes all AEs designated MedDRA Nervous System Class and selected AEs desgnated Psychiatric System Class (anxiety, anxiety disorder, insomnia, irritability, nervousness, sleep disorder).
**No Grade 4 nervous system events were reported in this study.

Malignancies

Because of ETV was found to be positive in rodent carcinogenicity studies, all malignancies and pre-malignant lesions occurring during the study were evaluated. A total of 11 malignant or pre-malignant lesions were diagnosed during Study 027. Case report forms and narrative summaries for each event were reviewed. These malignant and pre-malignant events are summarized in Table 10.1.2N.

Chronic HBV is known to increase the risk of HCC. In this study, 2 ETV subjects and 3 LVD subjects were diagnosed with HCC. Two of the HCC diagnoses were within a few weeks of beginning study treatment suggesting that these lesions may have been present at the time of study entry. One of the HCC (#122-50927) was considered by the investigator to be possibly related to study drug. Little is known about risk factors for other malignancy in the study population.

Table 10.1.2N: Subjects Reported to have Malignancies – Study 027

Patient ID (Site#-Subject#)	Age/Sex/Race	Study Drug (Days of Exposure/Obs)	Type of Malignancy	Additional Comments
Hepatic Malignancies				
12-51342	53/F/Asian	ETV 0.5 mg (291)	Hepatocellular carcinoma	History of Stage 3 fibrosis on pre-study biopsy
101-50558	46/M/White	ETV 0.5 mg (309)	Hepatocellular carcinoma	History of significant ethanol intake (pre-study)
40-50662	42/M/Asian	LVD 100 mg (40)	Hepatocellular carcinoma	History of bridging fibrosis on pre-study biopsy
88-50369	55/M/Asian	LVD 100 mg (22)	Hepatocellular carcinoma	

122-50927	43/M/White	LVD 100 mg (365/425)	Hepatocellular carcinoma	Baseline biopsy with Knodell fibrosis Score = 3 and cirrhosis at Week 48
Non-hepatic Malignancies				
5-50742	72/M/Asian	ETV 0.5 mg (322)	Gastric adenocarcinoma	History of gastric ulcer and gastritis
99-50677	70/F/White	ETV 0.5 mg (56)	Breast cancer (invasive ductal and lobular carcinoma)	
113-51000	39/F/White	ETV 0.5 mg (363/370)	Uterine adenocarcinoma, basal cell carcinoma	
58-51369	30/F/White	LVD 100 mg (325)	Breast (ductal) adenocarcinoma	
193-50490	66/F/White	LVD 100 mg (325)	Breast carcinoma in situ	
Pre-malignant or Unclassified Lesions				
102-50091	33/F/White	LVD 100 mg (138)	Actinic keratosis	

Source: Medical Officer's review of the clinical datasets.

Laboratory Abnormalities

Evaluation of clinical laboratory parameters was conducted by analyzing the proportion of subjects in each treatment group who experienced marked laboratory abnormalities during the study. Marked laboratory abnormalities were identified using a standardized table of Recommendations for Grading Acute and Subacute Adverse Events included in the study protocol (modified from WHO recommendations). The applicant evaluated laboratory abnormalities during both on-treatment and off-treatment periods; the Medical Officer focused on findings occurring while patients were receiving study drugs. In addition to evaluating marked laboratory abnormalities, the Medical Officer also assessed mean changes from baseline for selected laboratory tests.

Laboratory abnormalities were observed in almost all subjects in Study 027 since one of the study entry criteria was elevated ALT. Most laboratory abnormalities were transient and toxicity Grades 1 and 2. As might be expected in this study population, the most commonly observed laboratory abnormalities on-treatment were those related to liver dysfunction. Commonly identified laboratory abnormalities (all toxicity grades) included: elevated total bilirubin (35% of ETV subjects and 19% of LVD subjects), decreased albumin (7% ETV, 5% LVD), prolonged PT (38% ETV, 33% LVD), increased INR (31% ETV, 26% LVD), elevated amylase (27% ETV, 27% LVD), elevated lipase (30% ETV, 25% LVD), and fasting hyperglycemia (17% ETV, 16% LVD). Minor differences across the treatment groups were not clinically significant.

Among the 638 subjects who received treatment and for whom laboratory data is available, 259 (41%) were documented to have at least one laboratory abnormality ≥ Grade 3, 133 (41%) ETV subjects and 126 (40%) LVD subjects. Proportions of subjects experiencing ≥ Grade 3 abnormalities after baseline are summarized in Table 10.1.2O. Clinically significant or Grade 3 and 4 abnormalities in routine hematologic parameters were uncommon in both treatment groups.

Table 10.1.2O: Subjects On-Treatment Experiencing ≥ Grade 3 Laboratory Abnormalities – Study 027

Laboratory Parameter	ETV (N=325)	LVD (N=313)
ALT	45 (14%)	53 (17%)
Amylase	8 (2%)	5 (2%)
AST	15 (5%)	20 (6%)
Bicarbonate – low	3 (<1%)	3 (<1%)
Glucose – high	17 (5%)	11 (4%)
Glucose – low	2 (<1%)	2 (<1%)
INR	5 (2%)	4 (1%)
Lipase	17 (5%)	13 (4%)
Platelets	1 (<1%)	1 (<1%)
Potassium – high	2 (<1%)	3 (<1%)
PT	5 (2%)	3 (<1%)
Total bilirubin	5 (2%)	4 (1%)
Urine, blood	31 (10%)	27 (9%)
Urine, glucose	18 (6%)	17 (5%)
Urine, protein	3 (<1%)	3 (<1%)

Source: Medical Officer's review of the clinical datasets.

Mean changes in selected laboratory tests for patients with paired specimens at baseline and Week 48 are shown in Table 10.1.2P. The most striking changes were seen in ALT. Laboratory evidence of liver injury is one of the key findings in chronic HBV and abnormal ALT was one of the entry criteria for the study. Treatment with either ETV or LVD resulted in a similar significant decrease in ALT over 48 weeks of dosing. Mean changes in other laboratory parameters were generally too small to be clinically meaningful.

Table 10.1.2P: Change from Baseline for Selected Laboratory Tests – Study 027

Laboratory Parameter	ETV 0.5 mg (N=325)	LVD 100 mg (N=313)
ALT (IU)	N = 310	N = 297
Baseline	141	141

Week 48	32	41
Change from baseline	-109	-101
Creatinine (mg/dL)	N = 307	N = 295
Baseline	0.91	0.93
Week 48	0.92	0.93
Change from baseline	0.01	-
INR	N = 255	N = 256
Baseline	1.12	1.10
Week 48	1.06	1.06
Change from baseline	-0.06	-0.04
Total bilirubin (mg/dL)	N = 310	N = 296
Baseline	0.86	0.79
Week 48	0.84	0.75
Change from baseline	-0.01	-0.04

Source: Medical Officer's review of the clinical datasets.
N=number with paired specimens at baseline and Week 48 visit.

Additional evaluation of changes in serum creatinine was performed to assess the proportion of study subjects who experienced increases in creatinine from baseline of ≥ 0.3 mg/dL or ≥ 0.5 mg/dL. The applicant calculated the number of patients in each treatment group who developed "confirmed" increases in creatinine, defined as 2 consecutive values above the analysis cut-off. They identified 22 (7%) ETV subjects and 22 (7%) LVD subjects with confirmed creatinine increase ≥ 0.3 mg/dL above their baseline value and 2 (<1%) ETV and 2 (<1%) LVD subjects with confirmed increases ≥ 0.5 mg/dL above their baseline. In a slightly different analysis, this reviewer assessed the number of subjects with an increase in creatinine at any time. This analysis identified 44 (14%) ETV subjects and 36 (12%) LVD subjects with any creatinine value ≥ 0.3 mg/dL above baseline and 6 ETV and 11 LVD subjects with any creatinine value ≥ 0.5 mg/dL above baseline.

Reviewer's Comments:
Based on pre-clinical animal studies, ETV was not expected to have significant renal toxicity. However, many patients with advanced liver disease have some degree of renal dysfunction and one of the approved treatments for chronic HBV (ADV) has known renal toxicity. The analyses of creatinine conducted for this review were similar to those conducted for the review of ADV. While the applicant's analysis of "confirmed" increase in creatinine may be indicative of more significant changes in this parameter, this Medical Officer thinks that the more inclusive analysis may also be useful. It is possible that those patients with a single significant abnormality may be subjected to additional office visits or additional laboratory assessments.

In general, the applicant's analysis of laboratory abnormalities occurring in the off-treatment period did not identify significant differences compared to the on-treatment analysis except in the analysis of ALT and AST abnormalities. Off-treatment Grade 3 or

4 elevations of ALT were documented in 36 (12%) ETV subjects compared to 75 (29%) LVD subjects, a significant difference. Off-treatment Grade 3 or 4 elevations of AST were identified in 22 (7%) ETV subjects and 35 (13%) LVD subjects. These findings are consistent with the adverse event profile identifying increased ALT flares during the off-treatment period (see previous discussion of ALT flares) with ETV subjects experiencing flares late in the follow-up period.

Conclusions

Study 027 compared treatment of chronic HBV with ETV 0.5 mg daily to standard treatment with LVD 100 mg daily over 52 weeks of randomized, blinded treatment. The study enrolled 648 adult men and women with documented e antigen negative, chronic HBV with evidence of ongoing liver inflammation as measured by liver biopsy and elevated ALT. Prior treatment with IFN was allowed but previous LVD or other nucleoside analogues was prohibited. Blinded study dosing and safety monitoring continued through Week 52 at which time decisions to continue or discontinue study dosing were made based on results of virologic and biochemical testing conducted at Week 48. The study design allowed subjects who achieved HBV DNA by bDNA assay < LOQ and ALT level < 1.25 x ULN (< Grade 1 toxicity) to discontinue blinded treatment and continue follow-up off treatment for 24 weeks. The primary efficacy endpoint was measured by liver biopsy at Week 48 as well as a variety of virologic, biochemical, and composite secondary endpoints. The study was designed to determine non-inferiority of ETV to LVD but also planned for a second series of analyses to determine superiority of ETV if the first statistical step was passed. A very small proportion of randomized subjects failed to receive study drug or failed to complete the Week 48 clinical evaluation.

For the primary efficacy endpoint, histologic improvement was defined as $\geq$ 2 point decrease in Knodell necroinflammatory score and no worsening in Knodell fibrosis score at Week 48 compared to the pre-treatment liver biopsy. Analysis of the study results confirmed that ETV was superior to LVD in achieving the primary endpoint of histologic improvement with 70% of ETV subjects and 61% of LVD subjects meeting the endpoint criteria. Sensitivity analyses conducted by both the applicant and the FDA Statistical Reviewer supported the robustness of these results. Similarly, the treatment effect measured by the primary efficacy endpoint was observed consistently across subgroups based on gender, race, age, geographic region, and a variety of baseline disease covariates.

Review of key secondary endpoints also supported the efficacy of ETV compared to LVD. ETV was shown to be superior to LVD in all analyses evaluating changes in HBV viral load over 48 weeks regardless of which assay was used (bDNA or PCR). FDA review confirmed the applicant's conclusions that a greater proportion of ETV subjects than LVD subjects achieved HBV DNA < 400 copies/mL (91% vs 73%) and ETV subjects achieved greater mean decreases in HBV DNA by PCR (-5.2 log vs 4.7 log). Other key secondary endpoint analyses concluded that ETV was equivalent to LVD through 48 weeks included the proportion of subjects achieving normalization of ALT (76% ETV subjects, 68% LVD subjects) and the proportion with improvement in Ishak fibrosis score (36% ETV subjects, 38% LVD subjects).

In this study, the protocol-defined criteria for Composite Response included a virologic component (HBV DNA bDNA < 0.7 MEq/mL) and a biochemical component (ALT < 1.25 x ULN). The great majority of subjects in both treatment arms achieved Composite Response, 85% ETV subjects and 78% LVD subjects. Most of these subjects discontinued blinded study treatment and were followed off-treatment. Of the subjects who discontinued treatment per protocol, 48% of ETV and 35% LVD subjects maintained the Composite Response criteria. Only 3-4% of subjects discontinuing treatment according to protocol criteria maintained HBV DNA levels < 400 copies/mL. The study criteria for response clearly failed to accurately identify subjects in this population who could maintain a durable response to treatment.

The safety evaluation of ETV compared to LVD included review of data from 638 subjects who received at least one dose of blinded study drug in Study 027. Adverse events were extremely common, occurring in 76% of ETV subjects and 80% of LVD subjects. The pattern of common clinical and laboratory AEs documented in the study were similar across treatment arms and consistent with those expected in a population with chronic HBV. The most commonly reported AEs occurring on-treatment were headache, upper respiratory infection, upper abdominal pain, fatigue, influenza, and "common cold". Most of the AEs reported were mild or moderate in severity and judged to be not related to administration of study drugs. Severe or life-threatening AEs (Grade 3 or 4) occurred in 8% of ETV subjects and 12% of LVD subjects. Grade 3 or 4 AEs occurring in greater than 1% of either treatment group included: increased lipase (2% ETV, 2% LVD) and increased ALT (<1% ETV, 3% LVD). During the off-treatment follow-up period, AEs were reported by a smaller proportion of subjects in both treatment group, 51% of ETV subjects and 55% of LVD subjects. The pattern of AEs during the off-treatment period was similar to that seen during treatment except that elevated ALT were reported as AEs more frequently among the LVD subjects (7% ETV, 15% LVD). Other commonly reported AEs during the off-treatment period included headache, fatigue, nasopharyngitis/common cold, and upper respiratory infection.

Serious AEs occurring on-treatment were reported in small proportions of subjects in both treatment groups, 6% of ETV subjects and 8% of LVD subjects. No specific event predominated and none was reported in more than 2 subjects in a treatment group. During the off-treatment follow-up period, SAEs occurred in 5% of ETV subjects and 7% of LVD subjects. During this period, however, about 50% of the SAEs in both treatment groups were due to elevations of ALT. Only 2% of ETV subjects and 3% of LVD subjects discontinued study drug because of AEs. Of the 15 total discontinuations, 5 were because of elevated amylase and/or lipase or pancreatitis, 2 were due to diagnosis of HCC, and 2 were because of elevated ALT/AST. Two deaths were reported throughout the study, both in ETV-treated subjects.

Adverse events that were evaluated in more detail included nervous system or neurologic AEs, ALT flares, and malignancies. These events were of special interest based on either signals identified during animal toxicology studies (neurologic AEs and malignancies) or known complications of HBV and its treatment (ALT flares). Neurologic AEs were not identified in ETV-treated subjects significantly more frequently than in LVD-treated subjects regardless of whether the events were analyzed separately or collectively. Combined neurologic AEs of $\geq$ Grade 2 were documented in 15% of ETV subjects compared to 9% of LVD subjects, due to an

increase in a variety of events of moderate severity. The most common nervous system AE was headache, reported in 15% of ETV subjects and 17% of LVD subjects. In Study 027, malignant or pre-malignant lesions were diagnosed in 11 subjects, 5 ETV and 6 LVD subjects. To date, 2 subjects who received ETV and 3 subjects who received LVD have been diagnosed with HCC. ALT flares were very uncommon during treatment in either treatment arm, and none resulted in study drug discontinuation. Flares were more commonly documented during the off-treatment follow-up period, occurring in 8% of ETV subjects and 11% of LVD subjects.

Laboratory abnormalities were documented in almost all study subjects at some time during the study, not a surprising finding since elevated ALT was one of the entry criteria. Abnormalities ≥ Grade 3 were observed in 41% of study subjects, most commonly elevations of ALT or other liver function tests. The pattern of laboratory abnormalities documented during study treatment was similar for the 2 treatment arms. Mean ALT decreased significantly from baseline to Week 48 in both treatment groups, 109 IU in ETV subjects and 101 IU in LVD subjects. However, during the off-treatment period, Grade 3 or 4 ALT and AST increases were identified more often in the LVD group than in the ETV group. This could be related to an earlier pattern of rebound of HBV viremia in LVD subjects who had discontinued therapy after meeting the Week 48 Composite Response criteria.

Summary

- Study 027 supports the effectiveness of ETV in the treatment of nucleoside-naïve, e antigen negative patients with chronic HBV based on the primary endpoint of improvement in liver histology over a 48 week dosing period.

- Multiple virologic, biochemical, and composite endpoints also support the efficacy of ETV compared to LVD.

- In this study population, the safety and tolerability of ETV was similar to that of LVD over 48 weeks of dosing.

- Based on this study, it is not possible to conclude whether ETV has an adverse impact on neurologic AEs or the development of malignancies.

- The Composite Response criteria used in this study failed to identify a population of HBeAg negative patients who could sustain a durable response after discontinuing study drug. Although ALT flares were relatively common in these subjects, flare events were rarely accompanied by other signs or symptoms of worsening liver function.

10.1.3 Lamivudine-Refractory Patient Population: Studies 014 and 026 are summarized below. Please refer to Dr. Hammerstrom's review for efficacy analyses of these studies. The study demographics and safety data from patients in both studies who received ETV 1.0 mg were pooled by the applicant and compared to those from subjects in both studies who received LVD 100 mg. According to the applicant, no pregnancies were noted in studies 014 and 026, and no clinically relevant changes in vital signs or ECGs collected during the study were identified.

Study AI463014: A Randomized, Double-Blind Comparison of Three Doses of Entecavir vs. Lamivudine in Immunocompetent Subjects with Chronic Hepatitis B Infection with Viremia on Lamivudine Therapy

Study Objectives and Design: The study objective was to determine the antiviral activity and safety of three once-daily doses of ETV (0.1 mg, 0.5 mg, and 1.0 mg) administered for 52 weeks in subjects with chronic hepatitis B virus (HBV) infection with viremia while on lamivudine (LVD) treatment. The primary objective was to determine the proportion of subjects in each treatment group with HBV DNA levels below LLQ (0.7 MEq/mL [700,000 copies/mL or 2.5 pg/mL] by the bDNA assay) at Week 24. As a secondary objective, the dose-response relationship of the three ETV doses as measured by the change from baseline in HBV DNA levels by the Roche Amplicor PCR assay (LLQ = 400 copies/mL) was assessed at Week 24 to facilitate the selection of the ETV dose to be used in Phase III studies in a similar patient population.

This was a multi-national, randomized, double-blind study of three once-daily doses of ETV (0.1 mg, 0.5 mg, or 1.0 mg) as compared with continued LVD therapy (100 mg QD) for up to 76 weeks. Patient management decisions were made at Weeks 28 and 52 of blinded dosing, based on the virologic response at Week 24 and 48, respectively. The study was conducted by 49 principal investigators at 41 sites. This study was designed to demonstrate that one or more doses of ETV were superior to LVD for the primary endpoint (proportion of subjects with HBV DNA < LLQ by the bDNA assay at Week 24).

Subjects who achieved a virological response at Week 24 (≥ 1 $\log_{10}$ reduction in HBV DNA levels by the bDNA assay as compared with baseline levels) continued blinded therapy to Week 52. Subjects who experienced minimal virologic response (< 1 $\log_{10}$ reduction in HBV DNA and ≥ 10 MEq/mL by the bDNA assay) at Week 24 were discontinued from the blinded study treatment and either started on alternative therapy for HBV or were enrolled into the rollover study of ETV + LVD (study AI463901). Subjects who achieved a Complete Response at Week 48 (HBV DNA < LLQ by bDNA assay, normal ALT, and either loss of HBeAg or maintainance of HBeAg (-) state for subjects who were HBeAg (+) or (-) at baseline, respectively) discontinued study medication and were followed off treatment for up to 24 weeks to assess the safety and durability of response. Subjects who achieved a Partial Response at Week 48 (HBV DNA < LLQ by bDNA assay but HBeAg (+) or experiencing ALT elevations) continued blinded study treatment for up to an additional 24 weeks (to a total of 76 weeks) or until they were enrolled into the open label phase of this study. Subjects who did not demonstrate response at Week 48 (defined as HBV DNA $\geq$ LLQ by the bDNA assay) were to be discontinued from the

blinded treatment. Such non-responders as well as subjects who had a relapse off treatment (HBV DNA ≥ LLQ by bDNA assay or HBeAg (+), or ALT > 1.5X ULN on two determinations at least two weeks apart after achieving Complete Response) could either enroll in the BMS rollover study (AI463901) or start alternative anti-HBV therapy recommended by their physician. All subjects who discontinued from this study and did not enroll in another BMS-sponsored protocol were to be followed for safety for at least 12 weeks after the last dose of study drug. At the discretion of the investigator, subjects could be started on alternative, currently marketed anti-HBV therapy during the follow-up period after end of the blinded phase of study.

In all, a total of 182 subjects were randomized and 181 were treated, with 42, 47, and 47 subjects in the ETV 0.1 mg, 0.5 mg, and 1.0 mg groups, respectively, and 45 in the LVD group. The planned duration of the blinded portion of the study was up to 76 weeks. However, pending availability of the rollover protocol, some subjects were permitted to extend the blinded dosing period beyond 76 weeks. The maximum duration of blinded dosing in this study was 85 weeks.

Major inclusion criteria were: male and female subjects who were ≥ 16 years of age with chronic HBV infection (defined as either HBeAg (+) or (-) with documented HBV viremia on LVD therapy). HBV viremia was defined as one of the following HBV DNA measurements on two determinations at least two weeks apart while on LVD therapy: ≥ 10 pg/mL by the assay; ≥ 25 pg/mL by the assay, or ≥ 10 MEq/mL (≥35.4 pg/mL) by the bDNA assay.

Demographics: The majority of subjects were male (81%) and Caucasian (61%) or Asian/Pacific Islander (32%). The mean age was 46 years. Approximately 67% of subjects were HBeAg (+) at baseline. Out of the 182 subjects who were randomized, 172 (95%) completed 24 weeks of blinded dosing (40, 43, and 46 subjects for ETV 1.0 mg, 0.5 mg, and 0.1 mg, respectively, and 43 for LVD) and 138 (76%) completed 48 weeks of blinded therapy (39, 40, and 32 subjects for ETV 1.0 mg, 0.5 mg, and 0.1 mg, respectively, and 27 for LVD). A total of nine subjects (5%) discontinued therapy prior to Week 24 with four (2%) subjects discontinuing due to AEs. In all, 34 (19%) subjects discontinued blinded therapy between Weeks 24 and 48. The majority of such discontinuations occurred in the ETV 0.1 mg group and LVD group and was due to minimal virologic response.

Study AI463026: A Phase III Study of the Comparison of Entecavir to Lamivudine in Chronic Hepatitis B Subjects with Incomplete Response to Current Lamivudine Therapy

Study Objectives and Design: The co-primary study objectives were to determine the proportion of subjects in each treatment group who achieved: 1) Histologic Improvement: ≥ 2 point decrease in the Knodell necroinflammatory score and no worsening (≥ 1 point increase) in the Knodell fibrosis score on the Week 48 liver biopsy as compared to that performed at baseline; and 2) Composite Endpoint: HBV DNA levels < LLQ for the bDNA assay and normalization of serum ALT (<1.25X ULN) at Week 48.

A number of secondary efficacy endpoints were examined, including virologic (e.g. proportion of subjects with HBV DNA < 400 copies/mL by PCR assay at Week 48, and genotypic and phenotypic analyses for subjects with virologic rebound), serologic (e.g. proportion of subjects with loss of HBeAg ± appearance of HBeAb at Week 48), and biochemical (e.g. ALT normalization < 1.25X ULN at Week 48) parameters.

This was a multi-national, randomized, double-blind study of safety and efficacy of ETV (1.0 mg) as compared with continued LVD therapy (100 mg QD) for up to 96 weeks. Treatment response was determined by a number of assessments, including histologic, biochemical (ALT normalization), virological (reduction in HBV DNA levels), and serological (loss of HBeAg) parameters. Patient management decisions were made at Week 52 of blinded dosing and were based on the virologic and serologic (HBeAg) response at Week 48. The study was conducted by 84 principal investigators at 84 sites, of which 75 sites were involved in management of post-randomization study subjects.

Subjects who achieved a Complete Virologic Response (undetectable HBV DNA levels by bDNA assay and undetectable HBeAg levels) at Week 48 were discontinued from study medication and were subsequently followed off therapy for 24 weeks. Subjects who experienced a Partial Virologic Response (undetectable HBV DNA levels but detectable HBeAg levels) continued study medication until 96 weeks, or until Complete Virologic Response was achieved and then were followed off therapy for 24 weeks. Subjects who were deemed Virologic Non-Responders (detectable HBV DNA levels by bDNA assay) at Week 48 discontinued therapy and were offered the option of enrolling in a BMS rollover study (AI463901) or ETV Early Access Program. All subjects who did not enroll in another BMS-sponsored protocol were to be followed for safety every four weeks for 24 weeks after the last dose of study drug.

In all, a total of 293 subjects were randomized and 286 were treated, with 141 subjects in the ETV group and 145 in the LVD group. Major inclusion criteria were: male and female subjects who were ≥ 16 years of age with chronic HBV infection, HBeAg (+), HBsAg (+), and who had an incomplete response to LVD treatment (defined as persistently detectable HBV DNA by the bDNA assay after at least 36 weeks of LVD therapy, breakthrough viremia while on LVD, recurrence of HBV viremia following LVD discontinuation which persists following resumption of LVD treatment, or documented LVD resistant mutation and HBV viremia while on LVD therapy). Additional entry criteria included: evidence of chronic HBV infection as documented by liver biopsy within 52 weeks prior to randomization; HBV DNA ≥ 3.0 MEq/mL by the bDNA assay, and ALT between 1.3X and 10X ULN at screening and at least once within 12 weeks prior to screening with no intervening normal ALT values. Subjects with clinical or laboratory evidence of decompensated liver disease were excluded from study participation. HBV viremia was defined as one of the following HBV DNA measurements on two determinations at least two weeks apart while on LVD therapy: ≥ 10 pg/mL by the assay; ≥ 25 pg/mL by the assay, or ≥ 10 MEq/mL (≥ 35.4 pg/mL) by the bDNA assay.

Demographics: The majority of subjects were male (76%) and Caucasian (62%) or Asian/Pacific Islander (37%). The mean age was 39 years. Approximately 85% of subjects bore LVD-resistant HBV at baseline. Of the subjects who were randomized, 259 (88%) completed first

year of blinded dosing (133 for ETV and 126 for LVD). A total of 27 subjects (9%) discontinued therapy prior to Week 48 with nine (3%) subjects discontinuing due to AEs. Two subjects, both in the LVD group, discontinued blinded therapy before Week 48 due to treatment failure/lack of efficacy.

LVD-Refractory Study Population: ETV 1.0 mg vs. LVD 100 mg.

For the following analyses, data from patients in studies 014 and 026 and who received ETV 1.0 mg QD were pooled and compared with subjects in both studies who received LVD 100 mg QD.

Demographics:

Table 10.1.3A. Demographic Characteristics at Baseline: LVD-Refractory Subjects

	Treatment Regimen			
Characteristic	ETV 1.0 mg N = 183		LVD 100 mg N = 190	
Age (Years)				
Mean (SE)	41	1.1	41	1.0
SD	15		14	
Median	41		41	
Age (Years): N, %				
16 – 20	15	8	19	10
21 – 64	158	86	160	84
≥ 65	10	5	11	6
Gender: N, %				
Male	144	79	146	77
Female	39	21	44	23
Race: N, %				
White	109	60	122	64
Asian	69	38	64	34
Other	5	3	4	2
Region: N, %				
Asia	43	23	46	24
Europe	83	45	90	47
North America	44	24	41	22
South America	13	7	13	7

Source: NDA 21,797, Vol. 7, p. 43.

The applicant states that the demographic characteristics of the two study populations were similar. Except for the BMI, the numbers shown on Table XXX were confirmed by this Medical Officer. **[??BMI which table??]**

Table 10.1.3B: Baseline Characteristics – LVD-Refractory Subjects

Characteristic	Treatment Regimen			
	ETV 1.0 mg N = 183		LVD 100 mg N = 190	
Knodell Necroinflammatory				
N	135		135	
Mean (SE)	6.5	0.28	6.5	0.29
SD	3.23		3.43	
Median	7.0		7.0	
Knodell Fibrosis				
N	135		135	
Mean (SE)	1.7	0.10	1.8	0.10
SD	1.19		1.18	
Median	2.0		2.0	
Knodell Fibrosis: N, %				
0 (None)	7	5	10	7
1 (Portal)	81	57	72	51
3 (Bridging)	33	23	44	31
4 (Cirrhosis)	14	10	9	6
Ishak Fibrosis: N, %				
0 (No Fibrosis)	7	5	10	7
1	37	26	36	25
2	43	30	36	25
3	25	18	32	23
4	9	6	12	8
5	5	4	4	3
6	9	6	5	4
99 (Inadequate specimen)	6	4	7	5

Source:NDA 21,797, Vol. 7, p. 44 and pp. 206-207.

Table 10.1.3C: Virology and Serology at Baseline: LVD-Refractory Subjects

Characteristic	Treatment Regimen			
	ETV 1.0 mg N = 183		LVD 100 mg N = 190	
HBV DNA by bDNA (log_{10} MEq/mL)				
Mean (SE)	2.50	0.070	2.48	0.066
SD	0.951		0.911	
Median	2.65		2.59	
Min, Max				
Missing	0		0	
HBV DNA by PCR (log_{10} copies/mL)				
Mean (SE)	9.39	0.130	9.25	0.103
SD	1.760		1.419	

Median	9.34		9.26	
Min, Max	—		—	
Missing	0		0	
HBeAg: N, %				
Positive	163	89	174	92
Negative	20	11	16	8
HBeAb: N, %				
Positive	17	9	18	9
Negative	166	91	172	91
HBsAg: N, %				
Positive	183	100	190	100

Source: NDA 21,797, Vol. 7, pp. 209-210.

Table 10.1.3D. Baseline ALT Levels and LVD-Resistant Mutations – LVD-Refractory Subjects

	Treatment Regimen			
	ETV 1.0 mg N = 183		LVD 100 mg N = 190	
ALT: N, %				
< 1.25X ULN (Normal, as defined as applicant)	38	21	32	17
1.25 - < 2.6X ULN (Grade 1)	78	43	102	54
2.6 - < 5.1X ULN (Grade 2)	38	21	35	19
5.1 – 10X ULN (Grade 3)	25	14	11	6
> 10X ULN (Grade 4)	4	2	9	5
Missing	0		1	
ALT (U/L)				
Mean (SE)	127.7	9.67	126.7	11.04
SD	130.86		151.73	
Median	88.0		81.0	
Min, Max	—		—	
Missing	0		1	
LVD-resistance mutation: N, %				
Present	156	86	163	87
Absent	26	14	25	13
Missing	1		2	

Note: In the Clinical Safety summary of this NDA, the applicant defines LVD resistant mutations at codon 552 and/or codon 528. Please refer to Dr. Naeger's Microbiology review for additional analyses of LVD-resistant mutations.
Source: Adapted from NDA 21,797, Vol. 7, p. 212 and p. 218.

The baseline characteristics with respect to biochemical, histological, serological, and virological parameters were similar between the two treatment groups. The numbers shown in Tables 10.1.3B-10.1.3D were verified by the Medical Officer with minor, clinically insignificant differences between the applicant's analyses of HBV DNA levels (by bDNA and PCR assays)

and those by this Medical Officer. With respect to other biochemical parameters at baseline, the applicant states that the mean/SE values of albumin, total bilirubin, and prothrombin time for the ETV 1.0 mg group were similar to the corresponding values for the LVD 100 mg group; these findings were also confirmed by the Medical Officer.

Table 10.1.3E: Observation Time by Study Period: LVD-Refractory Subjects

		Observation Time (Weeks) Treatment Regimen	
Study Period	Summary Statistics	ETV 1.0 mg N = 183	LVD 100 mg N = 190
On Treatment	N	183	190
	Mean (SE)	70.2 (1.47)	52.3 (0.95)
	Median	71.0	53.0
	Min, Max	4.7, 108.1	8.3, 88.0
Off-Treatment Follow-up	N	56	31
	Mean (SE)	14.9 (1.25)	12.9 (1.36)
	Median	14.2	11.4
	Min, Max	1.0; 34.3	0.7, 27.7
24-Week Follow-Up	N	60	37
	Mean (SE)	16.6 (1.33)	15.2 (1.29)
	Median	15.7	14.3
	Min, Max	0.3, 47.9	0.7, 29.4
On Study	N	183	190
	Mean (SE)	81.0 (2.03)	55.9 (1.15)
	Median	76.7	53.4
	Min, Max	16.6, 177.4	8.7, 177.4

On Treatment: Start of dosing to earlier of EOD (end-of-dosing + five days) or last patient contact.
Off-Treatment Follow-up: EOD to earlier of start of alternative HBV therapy or last contact.
24-Week Follow-up: EOD to last patient contact.
On Study: Start of dosing to last contact.
Source: Adapted from NDA 21,797, Vol. 7, p. 174.

The numbers in Table 10.1.3E were confirmed by the Medical Officer. The applicant notes that the LVD-treated subjects had shorter on-study treatment periods. According to the applicant and as confirmed by this Medical Officer, this was most likely due to the hepatitis B-related treatment discontinuations among subjects with LVD-refractory viremia and who were given LVD during the study period.

Efficacy: Please see Dr. Hammerstrom's Statistical Review.

Safety:

Table 10.1.3F: Adverse Events Reported in ≥ 3% of Patients (in ETV On-Treatment Group) in the LVD-Refractory Population: All Grades, All Causality

System Organ Class Preferred Term (MedDRA 7.0)	On Treatment				Off Treatment			
	ETV 1.0 mg N = 183		LVD 100 mg N = 190		ETV 1.0 mg N = 56		LVD 100 mg N = 31	
	n	%	n	%	n	%	n	%
Any AE	156	85	155	82	26	46	14	45
Blood and Lymphatic Disorders	6	3	4	2	1	2	0	0
Cardiac Disorders	6	3	4	2	0	0	1	3
Ear and Labyrinth Disorders	5	3	6	3	0	0	1	3
Eye Disorders	6	3	7	4	1	2	0	0
Gastrointestinal Disorders	74	40	76	40	5	9	5	16
Abdominal Pain Upper	15	8	24	13	0	0	2	6
Diarrhea	13	7	14	7	1	2	0	0
Nausea	13	7	17	9	1	2	0	0
Dyspepsia	10	5	7	4	1	2	0	0
Abdominal Pain	8	4	12	6	1	2	0	0
Vomiting	8	4	5	3	0	0	0	0
Flatulence	6	3	1	<1	0	0	0	0
General Disorders	58	32	56	29	4	7	4	13
Fatigue	26	14	22	12	2	4	2	6
Pyrexia	16	9	7	4	0	0	0	0
Asthenia	7	4	8	4	1	2	1	3
Influenza like Illness	6	3	7	4	0	0	0	0
Hepatobiliary Disorders	7	4	11	6	0	0	2	6
Immune System Disorders	5	3	4	2	0	0	0	0
Infections and Infestations	73	40	74	39	11	20	5	16
Upper Respiratory Tract Infection	30	16	22	12	3	5	0	0
Nasopharyingitis	16	9	19	10	1	2	1	3
Influenza	7	4	10	5	2	4	0	0
Urinary Tract Infection	7	4	6	3	1	2	0	0
Bronchitis	6	3	4	2	1	2	0	0
Pharyingitis	6	3	3	2	0	0	0	0
Injury, Poisoning, and Procedural Complications	17	9	8	4	0	0	0	0
Investigations	36	20	39	21	8	14	5	16
Lipase Increased	8	4	4	2	0	0	2	6
Blood Bilirubin Increased	7	4	2	1	0	0	0	0
ALT Increased	6	3	20	11	4	7	2	6
AST Increased	6	3	9	5	3	5	2	6
Metabolism and Nutrition	14	8	14	7	1	2	0	0
Musculoskeletal and Connective Tissue Disorders	39	21	47	25	2	4	2	6

Myalgia	12	7	8	4	0	0	0	0
Arthralgia	10	5	12	6	0	0	2	6
Back Pain	8	4	11	6	1	2	0	0
Muscle Cramp	6	3	4	2	1	2	0	0
Neoplasms, Benign, Malignant, and Unspecified	6	3	4	2	0	0	0	0
Nervous System Disorders	54	30	52	27	2	4	0	0
Headache	35	19	34	18	1	2	0	0
Dizziness	14	8	11	6	0	0	0	0
Psychiatric Disorders	25	14	19	10	0	0	1	3
Insomnia	10	5	10	5	0	0	0	0
Renal and Urinary Disorders	17	9	17	9	2	4	0	0
Reproductive and Breast Disorders	7	4	4	2	0	0	0	0
Respiratory Disorders	47	26	33	17	6	11	0	0
Cough	20	11	17	9	0	0	0	0
Pharyngolaryngeal pain	13	7	3	2	3	5	0	0
Skin and Subcutaneous Disorders	27	15	24	13	1	2	1	3
Pruritis	7	4	5	3	0	0	0	0
Rash	6	3	4	2	0	0	0	0
Vascular Disorders	9	5	12	6	1	2	1	3
Hypertension	6	3	5	3	0	0	1	3

Source: Adapted from NDA 21,797, Vol. 7, pp. 310-329, pp. 477-480.

Table 10.1.3G: Adverse Events Reported in ≥ 3% of Patients (in either On-Treatment Group) in the LVD-Refractory Population: Grades 2-4, Treatment-Related

	On Treatment				Off Treatment			
System Organ Class Preferred Term (MedDRA 7.0)	**ETV 1.0 mg N = 183**		**LVD 100 mg N = 190**		**ETV 1.0 mg N = 56**		**LVD 100 mg N = 31**	
	n	%	n	%	n	%	n	%
Any AE	44	24	45	24	3	5	4	13
Gastrointestinal Disorders	7	4	10	5	0	0	1	3
Abdominal Pain Upper	1	<1	6	3	0	0	0	0
General Disorders	7	4	8	4	0	0	0	0
Fatigue	6	3	5	3	0	0	0	0
Investigations	20	11	20	11	3	5	3	10
ALT Increased	5	3	11	6	1	2	2	6
AST Increased	5	3	6	3	1	2	2	6
Lipase Increased	5	3	3	2	0	0	1	3
Nervous System Disorders	8	4	7	4	1	2	0	0
Headache	8	4	2	1	1	2	0	0

Source: Adapted from NDA 21,797, Vol. 7, pp. 465-469.

The numbers shown in Tables 10.1.3F and 10.1.3.G were confirmed by the Medical Officer with minor, clinically insignificant variations as compared to the applicant's analysis. It is noted by

the applicant and confirmed by the Medical Officer that there were relatively fewer subjects in both off-treatment groups as compared to on-treatment groups.

Table 10.1.3H: Subjects Reporting Adverse Events Resulting in Study Drug Discontinuation – LVD-Refractory

Patient ID Number	Treatment	Age/Sex/Race	Days on Study Drug	Adverse Event Resulting in Discontinuation	Relationship to Study Drug
Study 026					
14-80134	LVD	49/M/Asian	330	Acute hepatitis exacerbation (SAE)	Probably
36-80002	LVD	36/M/Pacific Islander	93	Increased ALT (Grade 4)	Probably
38-80151	LVD	58/F/White	293	Skin rash	Possibly
40-80348	LVD	34/F/Asian	294	Elevated liver enzymes (Grade 4)	Possibly
50-80413	LVD	36/M/Asian	224	Elevated ALT and AST (Grade 4)	Possibly
76-80206	LVD	58/M/White	125	Elevated lipase (Grade 3)	Probably
101-80042	LVD	46/M/White	397	Hepatitis B activation/Liver failure (Death)	Not likely
101-80384	LVD	29/F/White	168	Elevated ALT (Grade 4)	Possibly
102-80125	LVD	42/M/White	217	Hepatocellular carcinoma	Nor Related
109-80291	ETV	29/M/White	202	Fever, ankle arthritis, lymph node enlargement (SAE)	Not likely
125-80154	LVD	37/M/White	505	Elevated ALT/AST (Grade 4)	Possibly
131-80041	ETV	23/F/White	522	Elevated INR, PT (Grade 3)	Possibly
Study 014					
02-6240	ETV	41/M/Black	33	Elevated LFTs (Grade 3)	Probably
26-6043	ETV	42/M/White	44	Elevated amylase and lipase (Grade 3/4)	Possibly
39-6209	ETV	56/M/Black	Unknown	Chest pain (SAE)	Possibly
10-6073	ETV	65/M/White	553	Basal cell lesion	Unrelated
01-6002	LVD	46/M/White	280	Elevated LFTs (Grade 3/4)	Possibly
26-6042	LVD	40/M/White	75	Liver failure (SAE)	Not likely
26-6204	LVD	20/M/White	365	Elevated ALT (Grade 3/4)	Possibly
33-6217	LVD	66/M/White	81	Elevated LFTs (Grade 3/4)	Probably

Source: Medical Officer's review of the clinical datasets.

Hematology:

The applicant states that among these subjects, the majority of abnormalities in the hematological parameters (hemoglobin, WBC, neutrophils, platelets, prothrombin time, and INR) were Grades 1 or 2 in severity. In general, such abnormal values were noted with comparable frequencies between the two study treatments. The applicant states that Grade 3-4 hematologic abnormalities were infrequent for both treatments ($\leq 2\%$ while on ETV; $\leq 4\%$ while on LVD).

The most commonly observed hematological abnormalities while on study drug were prolongation of prothrombin time (ETV: 34%; LVD: 36%) and increased INR (ETV: 32%; LVD: 38%). The applicant attributes these observations to underlying hepatic dysfunction among study participants. The applicant also states that the proportion of subjects with PT and/or INR abnormalities was lower in the ETV arm as compared with the LVD arm at various timepoints during the 48 weeks of study drug treatment. The applicant attributes this trend to the lack of substantial improvement in LVD-refractory subjects with chronic HBV who continued treatment with LVD. This trend was confirmed by this Medical Officer but no tests of statistical significance were performed by the applicant.

Serum Chemistries:

Liver function tests: The applicant presents the following table to summarize abnormal liver function parameters:

Table 10.1.3I. Liver Function Elevations from Baseline and Albumin Abnormalities: LVD-Refractory Subjects

Event	# with Event / # with Measurement (%)							
	On Treatment				Off Treatment			
	ETV 1.0 mg N = 183		LVD 100 mg N = 190		ETV 1.0 mg N = 56		LVD 100 mg N = 31	
	n	%	n	%	n	%	n	%
ALT > 2X Baseline	23/183	13	63/189	33	17/53	32	8/26	31
ALT > 3X Baseline	8/183	4	31/189	16	13/53	25	5/26	19
ALT > 2X Baseline & > 10X ULN	4/183	2	21/189	11	4/53	8	4/26	15
ALT > 2X Baseline & bilirubin > 2X Baseline & > 2X ULN	1/183	<1	2/189	1	1/53	2	0/26	0
AST > 2X Baseline	18/183	10	64/189	34	15/53	28	8/26	31
AST > 3X Baseline	5/183	3	37/189	20	8/53	15	6/26	23
AST > 2X Baseline & > 10X ULN	3/183	2	8/189	4	3/53	6	1/26	4
Bilirubin > 2X Baseline	23/183	13	30/189	16	9/53	17	7/26	27
Bilirubin > 3X Baseline	6/183	3	14/189	7	4/53	8	3/26	12
Bilirubin > 2X Baseline & > 5X ULN	1/183	<1	1/189	<1	1/53	2	1/26	4
Albumin < 2.5 g/dL	0/181	0	3/187	2	0/52	0	0/26	0

Source: Adapted from NDA 21,797, Vol. 7, p. 98.

In general, these numbers were in accord with those obtained by the Medical Officer. Minor differences, especially with respect to AST/ALT elevations > 2X and > 3X baseline, were noted between the analysis presented by the applicant and that by this Medical Officer. However, such differences are unlikely to significantly alter the conclusions reached by the applicant.

The applicant notes that increased ALT was frequently observed in both treatment arms (ETV: 90%; LVD: 96%). The incidence of Grade 3 or 4 increases in ALT and AST during study drug treatment was higher for subjects in the LVD arm as compared to those in the ETV arm (ALT: ETV 35/813 [19%]; LVD 59/189 [31%]; AST: ETV 12/183 [7%]; LVD 37/189 [20%]). With respect to Grade 3 or 4 abnormalities in total bilirubin, alkaline phosphatase, and albumin (hypoalbuminemia), such abnormalities were infrequent in both study arms (≤ 3% of subjects in either treatment arm in all three parameters). As noted in Table 10.3.1I, fewer subjects in the ETV arm had ALT elevations during treatment.

During off-treatment follow-up periods, the applicant states that fewer ETV subjects had elevations of ALT and AST of any severity as compared with subjects that received LVD (ALT: ETV 19/53 [36%]; LVD 20/26 [77%]; AST: ETV 16/53 [30%]; LVD 19/26 [73%]) (NDA 21,797, Vol. 7, p. 96). However, in the opinion of this Medical Officer, the numbers in Table 10.1.3I suggest that AST/ALT elevations of varying severities occurred with relatively similar frequency in both study arms during the off-treatment phase. Moreover, it is noted by this Medical Officer that more subjects who received ETV were followed off-treatment (n = 56) than those who received LVD (n = 31).

Other serum chemistries:

Pancreatic enzymes:

The applicant states that the majority of on-treatment pancreatic enzyme elevations were Grades 1 or 2 in severity and occurred in comparable frequencies between the two arms (amylase: ETV 26%, LVD 28%; lipase: ETV 31%, LVD 36%). Similarly, the frequency of Grade 3 or 4 enzyme elevations were relatively low in both treatment arms (amylase: ETV 4%, LVD 4%; lipase: ETV 8%, LVD 7%). The applicant also examined on- and off-treatment elevations in amylase and lipase > 3X baseline in both treatment groups. The applicant notes that the incidence of on-treatment serum lipase elevations of >3X baseline was slightly higher in subjects on ETV than in LVD-treated subjects (ETV 18%; LVD 11%). However, off-treatment elevations in lipase were noted with comparable frequency in both groups (ETV 13%; LVD 12%).

The applicant notes that of the ten ETV-treated subjects who developed Grade 3-4 amylase or lipase abnormalities while on treatment, three had associated symptoms possibly consistent with pancreatitis (nausea, vomiting, abdominal pain) but none had received a clinical diagnosis of pancreatitis.

During the off-treatment follow-up phase, the applicant notes that pancreatic enzyme elevations (all grades) were noted in 10/48 (21%; amylase) and 4/24 (17%; lipase) subjects who previously

received ETV. Similarly, for LVD-treated subjects off-treatment, elevations in amylase and lipase were noted in 3/26 (12%) and 5/17 (29%), respectively. The incidence of Grade 3-4 elevations in these laboratory parameters during off-treatment was lower in ETV-treated subjects (amylase: 2%; lipase: 4%) as compared to LVD-treated subjects (amylase: 8%; lipase: 12%). The applicant states that the "frequent reports of pancreatic enzyme abnormalities in the off-treatment follow-up period suggests an etiology other than drug toxicity" (NDA 21,797, Vol. 7, p. 103). In the opinion of this Medical Officer, it is unlikely that pancreatic enzyme elevations post-study drug treatments are drug-related. However, the relatively small number of subjects who were followed off-treatment may limit the interpretation of these results to the general patient population with chronic HBV infection.

Renal function tests:

The applicant states that the incidence of on-treatment abnormalities in BUN and creatinine measurements was low and comparable between ETV and LVD-treated subjects. No subject reported a Grade 3 or 4 abnormality in either of these laboratory parameters during the on- or off-treatment phases. The applicant provides the following table:

Table 10.1.3J: Creatinine Increases from Baseline – LVD-Refractory Subjects

	# with Event / # with Measurement (%)							
	On Treatment				Off Treatment			
	ETV 1.0 mg N = 183		LVD 100 mg N = 190		ETV 1.0 mg N = 56		LVD 100 mg N = 31	
Creatinine Increase from Baseline	n	%	n	%	n	%	n	%
≥ 0.3 mg/dL	20/183	11	15/189	8	3/53	6	1/26	4
≥ 0.5 mg/dL	3/183	2	2/189	1	2/53	4	0/26	0

Note: Baseline for the follow-up period is the last laboratory value at end of study drug dosing.
Source: NDA 21,797, Vol. 7, p. 108.

The applicant states that the on-treatment creatinine increases were comparable between the ETV- and LVD-treated subjects but slightly higher than in the nucleoside-naïve population. In general, the numbers in Table 10.1.3J are in accord with analysis performed by the Medical Officer.

Electrolytes:

The applicant states that the frequencies of electrolyte abnormalities were comparable between the treatments. The most commonly reported abnormality (all grades) was hypocarbia (ETV: 27%; LVD: 30%; both among subjects who had measurements). The applicant states that there were no treatment discontinuations due to hypocarbia and none of the subjects with hypocarbia had clinical manifestations consistent with lactic acidosis syndrome **(SEE EARLIER SECTION IN REVIEW??)**. On-treatment Grade 3/4 electrolyte abnormalities were reported in ≤ 2% of subjects in either treatment arm.

During the off-treatment phase of the studies, hypocarbia (all grades) was reported in 6/40 (15%) of subjects in ETV arm and 3/17 (18%) of subjects in the LVD arm (among subjects who had measurements). Of these, none were Grades 3 or 4.

The applicant also examined abnormalities in glucose levels. Among LVD-refractory subjects on study drug, abnormal fasting glucose levels were comparable between the two treatment arms, including the incidence of on-treatment Grade 3-4 glucose abnormalities (≤ 3% in both arms). Among subjects whose fasting or non-fasting glucose was measured, on-treatment glucose levels ≥ 200 mg/dL were noted in comparable frequencies between the two treatment arms (ETV 6%, LVD: 10%). The incidence of off-treatment glucose levels ≥ 200 mg/dL was low on both treatment arms (ETV 2%, LVD 4%).

Urinalysis:

The applicant states that on-treatment abnormal readings in the urinalysis results were comparable between the two treatment arms. The most frequently reported abnormalities were hematuria (ETV: 45%; LVD: 40%) and proteinuria (ETV: 42%; LVD: 35%). Grade 3 or 4 hematuria was noted in 9% and 10% of subjects on ETV or LVD, respectively, while Grade 3 or 4 proteinuria was reported in 3% and 2% of subjects on ETV or LVD, respectively. During the off-treatment phase, proteinuria was the most frequently reported abnormality (10/47 or 21% in ETV arm, 2/23 or 9% in LVD arm) of which 2/47 in the ETV arm and 0/23 in the LVD arm were Grade 3 or 4.

These results have been confirmed by the Medical Officer. The difference in the number of subjects with proteinuria during off-treatment with ETV and LVD are noted. However, given the relatively small numbers of subjects in the off-treatment phase, this difference in the incidence of proteinuria is unlikely to be of clinical significance.

Study 014: Safety Review

To ensure that there were no safety-related issues as related to ETV doses used in Study 014, the applicant's safety analysis of this study are briefly summarized below. It should be noted that the safety data from patients in the ETV 1.0 mg and LVD 100 mg groups have been pooled with those of Study 026 and reviewed in the previous section of this Appendix.

Table 10.1.3K: Study 014: AEs (All Grades) in at Least 5% of Subjects in Any Treatment Group-On Blinded Treatment

System Organ Class/Preferred Term	ETV 0.1 mg (N = 47)		ETV 0.5 mg (N = 47)		ETV 1.0 mg (N = 42)		LVD 100 mg (N = 45)	
	#	%	#	%	#	%	#	%
Any AE	35	74	34	72	36	86	38	84
Gastrointestinal Disorders								
Abdominal Pain NOS	0	0	1	2	3	7	2	4
Abdominal Pain Upper	3	6	2	4	3	7	5	11

Diarrhea NOS	5	11	6	13	3	7	3	7
Dyspepsia	3	6	3	6	3	7	2	4
Nausea	2	4	4	9	2	5	3	7
Abdominal Discomfort	1	2	1	2	0	0	3	7
General Disorders								
Fatigue	9	19	7	15	7	17	6	13
Pyrexia	5	11	4	9	6	14	3	7
Influenza-like Illness	4	9	0	0	1	2	2	4
Infections and Infestations								
URI NOS	2	4	4	9	4	10	6	13
Pharyngitis	0	0	1	2	3	7	0	0
Nasopharyingitis	5	11	5	11	1	2	5	11
Investigations								
Lipase Increased	3	6	2	4	2	5	2	4
ALT Increased	3	6	3	6	1	2	4	9
AST Increased	3	6	1	2	1	2	3	7
Musculoskeletal/Connective Tissue								
Muscle Cramp	0	0	1	2	3	7	0	0
Arthralgia	3	6	7	15	2	5	2	4
Back Pain	2	4	9	19	2	5	3	7
Nervous System Disorders								
Headache	13	28	12	26	10	24	10	22
Respiratory Disorders								
Bronchitis NOS	0	0	1	2	5	12	2	4
Cough	2	4	4	9	3	7	3	7
Pharyngolaryngeal Pain	1	2	4	9	1	2	1	2
Skin Disorders								
Pruritis	1	2	0	0	3	7	0	0
Vascular Disorders								
Hypertension NOS	2	4	3	6	2	5	2	4

Source: NDA 21,797, Electronic Submission, BMS AI463014 Report, p. 178.

In general, the applicant states that the overall frequency of AEs was comparable for all four study groups while on blinded therapy (Table 10.1.3K) and during the post-blinded phase. Most of the AEs were Grades 1-2 in severity. Grade 3-4 AEs were also reported at comparable rates among all study groups (ETV arms: 21-26%, LVD arm: 20%) during blinded treatment. Lastly, there appears to be no dose-response relationship for treatment-emergent AEs in general or with respect to specific AEs.

Serious Adverse Events:
In the ETV 0.1 mg group one (2%) patients reported SAEs (esophageal hemorrhage and appendicitis) and in the ETV 0.5 mg group, two (4%) subjects reported SAEs (cholelithiasis, arthritis, and two cases of hepatic neoplasms) during the blinded study treatment. As a comparison, during the blinded study period, five (12%) of subjects in the ETV 1.0 mg group and three (7%) of subjects in the LVD group reported SAEs. During the off-treatment follow-up period, one subject in the ETV 0.1 mg group reported hepatic encephalopathy and mental status

changes that occurred five weeks following ALT/AST elevations and discontinuation of blinded therapy; these events were deemed as possibly related to study drug. In addition, during the 24 week follow-up period, one subject (AI463014-39-6039) in the ETV 0.1 mg group was hospitalized for hepatic failure and subsequently died. These events, as well as the deaths and malignancies noted during the study, are included in the Integrated Safety Review of the LVD-refractory population.

Treatment-discontinuing AEs:
During the blinded therapy phase, 13 subjects, including three (6%) in the ETV 0.5 mg group and three in the 0.1 mg group) discontinued blinded therapy due to AEs. In the ETV 0.1 mg group, such events were increased ALT, increased amylase, and increased lipase, whereas in the ETV 0.5 mg group, such events were increased lipase, abnormal liver function tests, hypoglycemia, and hepatic malignancy.

Laboratory Evaluations:
The applicant notes that the pattern and frequency of laboratory abnormalities (hematology, serum chemistries, and urinalysis) noted during the study were similar across the four treatment arms. The vast majority of such abnormal laboratory values were Grades 1-2 in severity. Given the underlying HBV disease in the study population, elevated ALT values were commonly noted. The applicant states that Grade 3-4 ALT elevations were noted in 11/42 (26%), 11/47 (23%), and 7/47 (15%) in the ETV 1.0 mg, 0.5 mg, and 0.1 mg groups, respectively, and 15/45 (33%) in the LVD group during the blinded treatment phase.

With respect to hepatitis B flares, defined as ALT elevations > 2X baseline and >10X ULN, a total of 11 (6%) of study subjects (3 (7%), 1 (2%), and 2 (45) in the ETV 1.0, 0.5, and 0.1 mg groups, respectively, and 5 (11%) in the LVD group) were noted to meet this criteria during blinded therapy. Of these 11 subjects, two had associated hepatic SAEs (hepatic encephalopathy, ascites/peritonitis) along with the ALT elevations. During the 24 week follow-up period, five events of HBV flares were noted (all in the ETV-treated subjects), four of which occurred during the off-treatment follow-up. One of these events resulted in hepatic failure and death during the 24-week follow-up in a subject who was treated with ETV 0.1 mg during the study and thereafter was receiving LVD.

Thus, based on the applicant's safety review as summarized above, this Medical Officer believes that there are no significant safety issues that appear to be related to the doses of ETV as administered in this study. One limitation of this interpretation is the relatively small patient population that was used for this study. Also, the safety findings of this study should be taken in the context of previously conducted ETV dose-finding studies; please see Dr. Bergman's Clinical Pharmacology review for additional details.

10.1.4 Study AI463038: A Phase II, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adding Entecavir to Current Lamivudine Therapy in HIV and HBV Co-Infected Patients Who Have Hepatitis B Viremia While on Lamivudine Treatment

Study Objectives and Design: The primary objective of this study was to compare the mean HBV DNA level (by PCR) in each treatment group at Week 24.

The interim study report in this NDA contains the 24-week efficacy and safety data. At the time of the report, this study was ongoing at 28 international sites. The investigators examined the safety and antiviral efficacy of ETV 1.0 mg QD as compared to placebo administered for 24 weeks to HIV-HBV co-infected adults with HBV viremia while on LVD-containing antiretroviral regimen.

This was a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of ETV in HIV-HBV co-infected subjects for 24 weeks during the blinded phase followed by open-label administration of ETV for an additional 24 weeks. Per protocol, a total of 60 subjects were to be randomized 2:1 to receive ETV 1.0 mg or placebo QD. All eligible subjects were to continue their ongoing LVD therapy (as 150 mg BID or 300 mg QD) throughout the study. During the course of the study, HBV DNA levels, HBV serologies, HIV RNA levels, CD4 cell count, and clinical and laboratory safety assessments were taken at specified intervals. Following the conclusion of the first 24 week period during which the study drug was administered in a double-blind manner, all subjects continued study participation into the 24 week open-label phase in which ETV 1.0 mg QD was administered to all subjects. Following the completion of the open-label phase, all subjects were given the opportunity to continue open-label administration of ETV.

Major inclusion criteria were: documented HIV/HBV co-infection, age $\geq$ 16 years, no evidence of HCV or HDV co-infection, on a stable antiretroviral regimen containing LVD for $\geq$ 24 weeks prior to enrollment; HIV RNA < 400 copies/mL at screening and $\geq$ 12 weeks prior to screening; documented HBV viremia (5 $\log_{10}$ copies/mL by PCR); HBeAg positive or HBeAg (-) and HBeAb(+); detectable HBsAg at screening and $\geq$ 24 weeks prior to screening visit; serum ALT not greater than 10X ULN at screening and at least once $\geq$ 12 weeks prior to screening; and compensated liver disease due to chronic hepatitis B.

The primary efficacy endpoint was the mean HBV DNA level by PCR at Week 24, based on a linear regression model adjusted for baseline HBV DNA level. A number of secondary efficacy endpoints were also examined, including the proportion of subjects with HBV DNA < 400 copies/mL at Week 24, mean HBV DNA level at Week 48, proportion of subjects with ALT normalization (defined as ALT < 1.25X ULN) at Weeks 24 and 48; HBV DNA mutations during the course of the study, and the proportion of subjects with seroconversion, i.e. loss of HBeAg and gain of HBeAb at Weeks 24 and 48. Efficacy data are reported for all subjects through the end of the blinded treatment phase.

The primary safety endpoint was the proportion of subjects who discontinued study drug due to clinical or laboratory AEs. A number of secondary safety endpoints were examined, including the proportion of subjects experiencing a rebound in HIV RNA levels (< 400 copies/mL to > 1000 copies/mL with confirmation within 4 weeks) at Weeks 24 and 48, the mean change from baseline in CD4 cell count at Weeks 24 and 48, and the proportion of subjects with > 2X and >3X increases in serum transaminases and bilirubin. Safety data are reported for all subjects through June 30, 2004. The applicant states that additional study data, including population pharmacokinetics and quality of life assessments, will be presented at a later date.

Demographics:
In all, 109 subjects were enrolled, of which 41 were not randomized; the most common reason was "subject no longer meets study criteria." The remaining 68 subjects were randomized to receive ETV 1 mg or placebo. Because 22 out of 24 sites randomized fewer than six subjects per site (i.e. the block size for the protocol-specified 2:1 randomization scheme), the final ETV: placebo ratio was nearly 3:1.

Most of the subjects completed the blinded treatment phase (ETV: 48 subjects (94%), placebo: 17 subjects (100%)). During the blinded treatment, two subjects (4%) in the ETV arm and none in the placebo arm discontinued due to an AE, and one subject (2%) in the ETV group discontinued to lack of treatment efficacy. A total of 48 (94%) subjects in the ETV arm and 17 (100%) subjects in the placebo arm participated in the open-label treatment phase of the study.

The majority of the treated subjects were male (96%) and Caucasian (85%). The mean age of the study population was 41 years. Approximately 50% of subjects were from South America, while the remaining subjects were from Europe (35%) and North America (15%). In general, the treatment arms were balanced with respect to demographic characteristics.

The distribution of baseline characteristics with respect to HIV and HBV infections were similar between the ETV and placebo treatment groups, including: mean HBV DNA levels (9.13 vs. 9.12 $\log_{10}$ copies/mL, respectively); mean HIV RNA levels (2.15 vs. 2.03 $\log_{10}$ copies, respectively); the proportion of subjects with HIV RNA levels < 50 copies/mL (31% and 29%, respectively) and < 400 copies/mL (86% and 94%, respectively); mean CD4 cell count (508 and 520 cells/mm^3, respectively); HBeAg seropositive status (98% and 100%, respectively); and HBsAg seropositive status (100% in both arms). The applicant notes that in 80% of the study population, at least one of the following antiretroviral agents was co-administered with study drug: nevirapine, ritonavir, lopinavir, stavudine, and didanosine.

Efficacy: According to the applicant, at Week 24, the mean HBV DNA levels for ETV and PLB groups were 5.52 and 9.27 $\log_{10}$ copies/mL, respectively. The estimated difference, when adjusted for baseline levels, in the reduction of mean HBV DNA levels (ETV – PLB) was -3.76 $\log_{10}$ copies/mL (95% CI: [-4.49, -3.04]; $p < 0.0001$). Only 3 ETV subjects (6%) and no PLB subjects achieved HBV DNA levels < 400 copies/mL at Week 24. HBeAg loss and seroconversion at Week 24 occurred in one subject in the ETV arm and none in the PLB group. Lastly, the applicant notes that ALT normalization (< 1.25X ULN) occurred in 11/30 (37%) and

1/7 (14%) of subjects treated with ETV and PLB, respectively, and who had baseline ALT levels ≥ 1.25X ULN. These results were confirmed by the FDA Statistical Reviewer.

Safety:

Serious Adverse Events, Deaths, Pregnancies:
No deaths or pregnancies were noted in the interim report. One subject had SAEs during the blinded treatment phase. Subject AI463038-34-30030, who received ETV, experienced hepatic encephalopathy and esophageal varices on Day 5 and Day 44 of study treatment, respectively. Four subjects, all of whom had received ETV during the blinded phase, experienced SAEs during open-label treatment. Among these four subjects, one subject each had an acute myocardial infarction, esophageal varices (same patient that had this SAE during the blinded phase), testicular neoplasm (spermatocystic seminoma), and pneumonia. Lastly, one subject had SAEs (elevated hepatic enzymes and elevated blood bilirubin levels) during the 24 week follow-up phase and was discontinued from study drug treatment. None of the SAEs were considered to be related to study medication.

Treatment discontinuations due to AEs:
Two subjects (4%) in the ETV arm and none in the placebo arm discontinued study therapy due to AEs. One subject did so due to elevated liver function tests during the 24 week follow-up phase (see SAEs, above). The other subject discontinued due to Grade 3/4 transaminases. Neither event was deemed to be related to study drug.

AEs:
During the blinded phase of the study, the frequency of AEs in the ETV arm was similar to that in the placebo arm (86% and 82%, respectively). The most frequently reported AEs (occurring in ≥ 10% of subjects in the ETV group) and the corresponding rates for the placebo group were: headache (14% and 18%, respectively), nasopharyingitis (10% and 12%, respectively), increased ALT (10% and 0%, respectively), and increased AST (10% and 0%, respectively). During the open label phase of the study, the only AEs that were reported in more than two subjects were diarrhea and influenza (four subjects each) and fatigue and increased lipase (three subjects each). According to the applicant, a review of medical terms to identify lactic acidosis syndrome /hyperlactatenemia or hepatic steatosis up to the interim report preparation identified no cases of either event.

The interim study report contains no formal analyses of ECGs or vital signs that were measured during the study.

Laboratory Abnormalities:
The applicant notes that elevated LFTs were noted in both treatment groups. Otherwise, non-hepatic laboratory values of Grade 3 or 4 were noted infrequently in both treatment groups during the blinded and open-label treatment periods.

Table 10.1.4A: Summary of AEs and Laboratory Abnormalities During Blinded Treatment

Event	Treatment Regimen			
	ETV 1.0 mg N = 51 n (%)		Placebo N = 17 n (%)	
Any AE	44	86	14	82
Any Severe AE (grades 3-4)	10	20	2	12
Any SAE	1	2	0	0
Treatment-emergent Grade 3-4 ALT[a]	7	15	1	6
ALT > 2X Baseline	13	26	4	24
ALT > 3X Baseline	7	14	2	12
AST > 2X Baseline	12	24	4	24
AST > 3X Baseline	7	14	0	0
Total bilirubin > 2X Baseline	8	16	1	6
Total bilirubin > 3X Baseline	2	4	0	0
ALT > 2X Baseline & total bilirubin > 2X Baseline & > 2X ULN	1	2	0	0

a: Grade 3-4 ALT elevations in subjects with baseline ALT < 5X ULN: N = 47 for ETV, N = 17 for placebo.
Source: Adapted from NDA 21,797, Study AI463038 study report, p. 10.

Table 10.1.4B: Summary of AEs and Laboratory Abnormalities During Open-Label Treatment

Event	ETV 1.0 mg N = 65 n (%)	
Any AE	37	57
Any Severe AE (grades 3-4)	5	8
Any SAE	4	6
Treatment-emergent Grade 3-4 ALT[a]	3	5
ALT > 2X EOD	8	13
ALT > 3X EOD	4	7
AST > 2X EOD	7	11
AST > 3X EOD	2	3
Total bilirubin > 2X EOD	4	7
Total bilirubin > 3X EOD	1	2
ALT > 2X EOD & total bilirubin > 2X EOD & > 2X ULN	0	0

a: Grade 3-4 ALT elevations in subjects with baseline ALT < 5X ULN: N = 47 for ETV, N = 17 for placebo.
EOD: Last available laboratory value at end of blinding dosing; N = 61.
Source: Adapted from NDA 21,797, Study AI463038 study report, p. 11.

With respect to other laboratory parameters, during the blinded and open-label phases of the study, the applicant notes that the vast majority of abnormal laboratory values were mild/moderate (Grade 1-2) in severity. These parameters include hematology, pancreatic enzymes, serum chemistries including electrolytes, and urinalysis.

Specific Safety Issues:
With respect to the maintained suppression of HIV RNA levels, no subject in the study developed a confirmed HIV virologic rebound. No clinically significant change in mean HIV RNA levels were noted during the blinded dosing state and at the time of the interim report preparation, no such event had been noted during the open label treatment. No clinically significant changes in CD4 cell counts were noted during blinded or open-label treatment periods.

ALT flares (defined as ALT levels > 2X baseline and > 10X ULN) were noted in two ETV-treated subjects and none in the placebo-treated subjects during the blind treatment phase. At the time of the interim study report preparation, no ALT flares had been reported during the open-label treatment.

With respect to neurologic AEs, the overall frequency of selected events during the blinded treatment period was 14% in ETV-treated subjects and 24% in the placebo-treated period. The most common neurologic AE was headache (14% in subjects treated with ETV and 18% of subjects given placebo). No other neurologic AEs were reported in more than one subject and no subject experienced Grade 3/4 neurologic AEs. During the open-label treatment period, only one subject reported a neurologic event (headache).

In general, the assessment of study data by this Medical Officer confirmed the findings of study 038 as presented by the applicant.

10.1.5 AI463015: A pilot study of the safety, pharmacokinetics, and antiviral activity of open-label entecavir in liver transplant recipients re-infected with hepatitis B virus

Protocol Study Design

This study was designed as a multinational, open-label study to evaluate the use of ETV at a dose of 1 mg in liver transplant recipients with recurrent HBV infection who could be treated in the out-patient setting. The primary objectives of the study were to assess the safety of ETV and to assess the PK profile of ETV after the first dose and at steady state when the drug was given in combination with cyclosporine or tacrolimus. Measurements of treatment response were considered secondary objectives.

Clinically stable liver transplant recipients who were more than 100 days post-transplant were recruited for the study if they had recurrent HBV viremia in spite of anti-HBV prophylaxis. Inclusion in the study required that subjects be between 18 and 65 years of age, on stable doses of cyclosporine or tacrolimus for at least 4 weeks, have documented HBV re-infection (or recurrence) in spite of prophylaxis as evidenced by detectable HBV DNA or documented viremia despite approved anti-HBV therapy for chronic HBV post-transplant, and have compensated liver disease and acceptable renal function. Major exclusion criteria included: co-infection with HIV, HCV, or HDV, ongoing acute opportunistic infection, recent history of pancreatitis, requirement for nephrotoxic drugs (excluding immunosuppressive medications) or hepatotoxic drugs, current alcohol or drug abuse, screening serum alpha fetoprotein > 100 ng/mL, and current evidence of ascites (requiring paracentesis), hepatic encephalopathy, or variceal bleeding. Subjects were prohibited from enrolling if they had previously received ETV. Subjects could be male or female but all sexually active subjects had to agree to use a reliable method of contraception during the study.

Study subjects who met the entry criteria were enrolled in the study and began ETV 1 mg taken once daily. Subjects were instructed to take their ETV dose on an empty stomach, preferably at the same time each day (suggested time was 10:00 AM). At the beginning of study, subjects discontinued any other oral anti-HBV treatment but were allowed to continue hepatitis B immune globulin prophylaxis. Subjects were supposed to remain on stable doses of cyclosporine or tacrolimus throughout the study.

Subjects were re-evaluated at multiple time-points during the study and management decisions were based on these assessments. The protocol-defined management guidelines were considered optional to provide local physicians with maximal flexibility in caring for a difficult patient population. According to the protocol-defined algorithm, subjects who failed to achieve a ≥ 1 log decrease in HBV DNA by bDNA assay by Week 12 or who had HBV DNA detectable by the bDNA assay at Week 24 could elect to discontinue ETV treatment. Subjects discontinuing study could receive other treatment as recommended by their physician or could enroll in Study 901 (the rollover protocol evaluating combination ETV+LVD). Subjects discontinuing ETV were to be followed for 12 weeks. Subjects with undetectable HBV DNA by bDNA at Week 24 continued ETV dosing until Week 48. At Week 48, subjects were re-evaluated and could either

continue or discontinue ETV based on criteria similar to those at Week 24. Subjects could continue ETV through Week 104 or until a separate open-label protocol was available.

On Day 1 subjects received their first dose of ETV at the research facility followed by intensive PK sampling pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post-dose. Similar intensive PK sampling was performed on Day 14 (steady state). Random PK sampling was obtained after dosing at Weeks 4, 12, 24, 36, and 48.

Study subjects were evaluated every 4 weeks during the first year of dosing and monitored with a battery of clinical and laboratory assessments. Clinical AEs were recorded at each study visit throughout the study and graded according to severity using a standardized toxicity grading system. Clinical AEs were also evaluated by the investigator according to perceived relationship to study drug (certainly, probably, possibly, not likely, or not related). Serious AEs and deaths were also identified and recorded. Subjects who developed an SAE or other dose-limiting toxicity were to have a blood sample collected for ETV levels. Laboratory abnormalities were also graded according to the standardized toxicity guidelines. Female subjects had pregnancy testing at every study visit. Laboratory testing other than HBV DNA measurement was conducted at the local sites.

Serial liver biopsies were recommended but not required for this study. The primary measurement used to evaluate efficacy was serum HBV DNA by bDNA assay performed at baseline and Weeks 12, 24, 36, 48, and 96. HBV DNA was also measured using the — — PCR assay — , with LOQ of — copies/mL. Pre-specified HBV DNA analysis was done using a lower cut-off limit of 400 copies/mL in order to be consistent with other studies. The PCR assay was performed at baseline and at Weeks 12, 24, and 48 if the HBV DNA level by bDNA assay was undetectable and then at additional timepoints at Weeks 64, 80, and 96. HBV serologic markers were assessed at specified intervals. Serum ALT levels were measured at each visit as part of the safety evaluation but were analyzed for efficacy at Weeks 24 and 48. Genotypic and phenotypic analyses for resistance were performed at baseline and any time a subject experienced a confirmed viral rebound of $\geq$ 1 log while on ETV. All HBV DNA analyses were conducted at a central laboratory —

Amendments

This non-IND protocol was finalized in December, 1999. Three protocol amendments were incorporated into the protocol after that time. Key revisions included in the amendments are summarized below.

Amendment 1 (June 15, 2000)
The primary revision proposed in this amendment was to include guidelines for the management of subjects who developed > Grade 2 neurologic AEs or > Grade 3 headache or change in pattern of headaches. It also incorporated updated information regarding Study 004 and included St. John's wort as a prohibited medication during study.

Amendment 2 (February 27, 2001)
This amendment provided subjects the opportunity to enroll in Study 901 (combination treatment with ETV+LVD) if they did not meet criteria for virologic response. The amendment specified that subjects rolling into Study 901 would be followed in that study and not included in 24 week post-dosing follow-up for Study 015. It also allowed subjects completing 48 weeks of therapy to continue for an additional 48 weeks

Amendment 3 (April 15, 2002)
This amendment to the protocol allowed an extension of dosing for subjects who were responding to ETV treatment at Week 96. Subjects remaining on ETV at Week 96 were to undergo another evaluation with management based on results of HBV DNA levels. Subjects with continued response to ETV at this evaluation were also eligible to enroll in Study 901 (the rollover protocol) or Study 900 (the open-label, compassionate access program).

A late change in the central laboratory used for the HBV DNA determinations necessitated a change in the PCR assay used. The original protocol specified use of the HBV DNA Amplicor PCR assay. Because the originally planned central laboratory was not available at the time the study started, HBV DNA samples were sent to
and their assay was the PCR, as noted above. Since the same assay was used throughout the study, the change in laboratory and assay had no impact on results.

Post Hoc Changes

An analysis of ALT flares and hepatic SAEs was not originally planned for Study 015. Because of special interest in these events, an analysis of the events was included in the study report. Similarly, because of increasing understanding of the mutations associated with ETV resistance and the association with LVD resistance, HBV genotype was evaluated retrospectively for all subjects at baseline and at later time-points as available.

Study Results

Disposition

A total of 10 liver transplant recipients were enrolled in Study 015 and 9 were treated with ETV 1 mg once daily. Mean time on ETV treatment in the study was 131 weeks (range 92 to 164). All 9 subjects completed study treatment and 7 were later enrolled in either the rollover protocol or the open-label compassionate access program.

Demographics and Baseline Disease Characteristics

The 9 subjects enrolled in the study were recruited from the U.S., Canada, Germany, and Australia. The mean age was 53 (range 43 to 64), 8 were male, 6 were white and 2 were Asian (one listed as "other").

All subjects enrolled in Study 015 were positive for HBsAg. Five subjects were HBeAg positive and 4 were HBeAg negative. Mean log HBV DNA was 3.25 by bDNA assay and 8.92 by PCR assay. Mean ALT for the group was 94 U/L, mean albumin was 4.0 g/dL, mean total bilirubin was 0.82 mg/dL, mean creatinine was 1.3 mg/dL, and mean INR was 1.3. All of the subjects enrolled had a history of prior LVD treatment but none had received prior IFN consistent with their pre-transplant diagnosis of cirrhosis. One subject had a past history of breast cancer treated years before study and one subject had a pre-transplant diagnosis of HCC. All of the subjects were receiving some type of immunosuppressive therapy following transplant; 5 subjects received cyclosporine and 4 received tacrolimus.

Efficacy

As noted in the Study Design, assessment of efficacy was considered a secondary objective of the study. The secondary efficacy evaluations reviewed by the Medical Officer included change from baseline in HBV DNA PCR assay, proportion achieving HBV DNA < 400 copies/mL, and change from baseline in ALT. Since this was a small, open label study, there was no comparison of efficacy to another treatment.

The applicant states that the mean decreases in HBV DNA levels from baseline to Weeks 24 and 48 were 3.62 log and 3.90 log, respectively. None of the subjects on study achieved HBV DNA < 400 copies/mL by Week 48 of study dosing. One subject reached the < 400 copies/mL cut-off at Week 112. These calculations were confirmed by the Medical Officer. The applicant notes that 8 of 9 subjects achieved $\geq$ 2 log decrease in mean HBV DNA at Week 24 and all 9 achieved $\geq$ 2 log decrease at Week 48. Subject #05-2004 had positive HBeAb at Week 48 and again at Week 124 and at the later time-point also had a negative HBsAg and a decrease in HBV DNA to < 400 copies/mL. This appears to represent a late but real seroconversion associated with virologic response. One other subject had loss of HBeAg and gain of HBeAb representing seroconversion but had a later rebound in HBV DNA levels.

Mean baseline ALT in the study cohort was 94 U/L. Over the course of the study the mean ALT for the cohort decreased to 42 U/L at Week 24 and to 40 U/L at Week 48. This represents a mean decrease in ALT of 54 U/L over 48 weeks of study drug dosing. Four of 9 subjects achieved normalization of ALT (< 1 x ULN) at Week 48.

Four of the 9 subjects had liver biopsies performed at both baseline for the study and at a later time-point. According to the applicant, 2 subjects achieved the criteria for histologic improvement ($\geq$ 2 point decrease in Knodell necroinflammatory score with no worsening in Knodell fibrosis score) at a Week 24 biopsy and a third subject achieved this endpoint at Week 84.

HBV isolates were evaluated for ETV and LVD resistance mutations in all subjects at baseline and at later time-points. Baseline isolates from all subjects were documented to be resistant to LVD. One subject had specimens that were inconsistent and suggestive of laboratory cross-contamination; this subject was considered unevaluable. Among the 8

subjects who had evaluable genotype results, one subject developed ETV resistance mutations by Week 48, one subject developed mutations by Week 96 and 5 subjects developed resistance mutations during the 3rd year of ETV dosing. ETV-associated resistance mutations were identified at the same time as viral rebound in 2 subjects and 8 to 51 weeks before viral rebound in 4 other subjects. One subject did not demonstrate viral rebound in spite of ETV-resistance mutations through the end of study observation. One subject (#05-2004, with late seroconversion) maintained virologic suppression and no evidence of genotypic resistance for the study period.

Safety

Adverse Events

All 9 subjects participating in the study experienced at least one AE. The most common AE's included: headache (5), diarrhea (4), depression (3), cough (3), pyrexia (3), fatigue (3), and arthralgia, increased creatinine, bronchitis, dyspnea, nasopharyngitis, peripheral edema, rash, tremor, and upper respiratory tract infection (2 each). Events that were Grade 3 or 4 in intensity occurred in 4 subjects and none were considered related to study drug. These AEs included: fever with bactermia, dehydration, renal neoplasm, and kidney stone. Six subjects experienced AEs that were considered possibly, probably, or certainly drug related including 3 with headache and 2 with arthralgia.

Serious Adverse Events

Two study subjects experienced SAEs during the study. Subject #15-2004, a 60 year old male, who had received 2 liver transplants was hospitalized because of fever, bacteremia with E. coli, and a liver abscess. He was treated with antibiotics and recovered and continued his ETV throughout the event which was considered unrelated to study drug. Subject #16-2010, a 46 year old male with a history of liver transplant because of cirrhosis and HCC, was diagnosed with a new kidney tumor on Day 723 of study drug dosing. The tumor was found at the time of routine follow-up CT after his liver transplant. It was removed surgically and no evidence of metastasis was identified. Study drug was not interrupted during the SAE and it was considered not likely related to ETV use.

Deaths

There were no deaths during the study.

Adverse Events Resulting in Study Drug Discontinuation

There were no discontinuations of study drug because of adverse events. Only a single subject interrupted treatment (6 day interruption) because of an increased creatinine.

There were no pregnancies reported during the study.

Adverse Events of Special Interest

Three types of AEs will be reported on specifically: acute exacerbations of hepatitis or ALT flares, nervous system or neurologic AEs, and malignancies. These events were of special interest during the ETV development program either because of their potential seriousness in this population or because of safety signals detected in animal toxicology studies.

There were no subjects in this study who experienced an ALT flare defined as an ALT > 2 x the baseline value and 10 x the ULN. The only hepatic SAE occurred in the subject who had a documented liver abscess (not reported by the applicant as a hepatic SAE) mentioned above.

Six of the 9 subjects in study reported a nervous system AE at some time while receiving ETV. Five subjects reported headaches, one of whom had a history of chronic headaches (migraine). Three of the 5 subjects reported headache were also receiving tacrolimus, a drug associated with headache. Two subjects described having a tremor and one of these subjects also reported dizziness.

One subject was reported to have a new diagnosis of malignancy during the study period. This subject (#16-2010) was described above (Serious Adverse Events section). Records of tumor histology were not available. His tumor was described as "kidney tumor."

Laboratory Findings

As might be expected in this population, many of the subjects had laboratory abnormalities at baseline or experienced laboratory abnormalities while receiving ETV. Grade 3 or 4 laboratory abnormalities were relatively uncommon in spite of the advanced disease of the subjects. As shown in Table 10.1.5A, the most commonly reported laboratory abnormalities were in liver function tests (ALT and AST), and pancreatic tests (lipase and amylase). No subject interrupted study drug because of clinically significant laboratory abnormalities. The applicant notes that all subjects who had significant abnormalities of glucose were known to have a history of diabetes.

Table 10.1.5A: Laboratory Abnormalities Observed in Study 015

Laboratory Parameter	Grades 1-4 Toxicity (N = 9)	Grades 3-4 Toxicity (N = 9)
Hemoglobin	1 (11%)	0
Neutrophils	2 (22%)	2 (22%)
Platelets	5 (56%)	1 (11%)
INR	3 (33%)	2 (22%)
ALT	8 (89%)	1 (11%)
AST	8 (89%)	1 (11%)

Total bilirubin	3 (33%)	0
Amylase	7 (78%)	1 (11%)
Lipase	6 (67%)	2 (22%)
Creatinine	7 (78%)	0
Glucose – high	5 (56%)	2 (22%)

Source: Medical Officer's review of the electronic datasets

Pharmacokinetic Evaluation

One of the primary objectives of Study 015 was to characterize the PK profile of ETV in subjects post-liver transplant. The exposure of ETV in this population was about 2 times that reported in healthy adults. This difference in exposure was most likely attributable to differences in renal function in the transplant recipients. Tacrolimus and cyclosporine levels were not reported in the study. For a more detailed description of the PK in liver transplant recipients, refer to the Clinical Pharmacology Review by Dr. Kim Bergman.

Conclusions

Study 015 was designed as an open-label, pilot study of ETV in liver transplant recipients who were > 100 days post-transplant and receiving a stable regimen of immunosuppressive medication. The size of the study does not allow definitive conclusions to be made regarding the safety and efficacy of ETV in this study population. ETV appeared to be relatively well-tolerated. Although a majority of subjects in this study reported headaches, it is not possible to establish whether these events were related to ETV use. In this study, no additional safety issues were identified compared to those seen in non-transplant subjects.

Use of ETV resulted in decreased HBV DNA levels in the study subjects as measured by both bDNA and PCR assays. Mean HBV DNA levels decreased by 3.90 log at Week 48 as measured by the PCR assay. Although no subjects achieved an HBV DNA level < 400 copies/mL by Week 48, one had a late seroconversion and sustained response until the end of study observation. Mean ALT levels decreased during the study and 4/9 subjects achieved normalization of ALT at Week 48.

ETV may be a reasonable treatment option for patients who are post-liver transplant and have recurrent HBV viremia and limited treatment options but additional data are needed to characterize the response to treatment and safety in this population.

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/s/

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3/29/05 11:53:30 AM
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Clinical Reviewers recommend approval.

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