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TABLE OF CONTENTS

TITLE PAGE. 1

TABLE OF CONTENTS 2

LIST OF TABLES 5

LIST OF FIGURES. 6

1 OVERVIEW 7

2 INTRODUCTION AND THERAPEUTIC RATIONALE 11

2.1 Target Disease and Currently Available Treatment Options 11

2.2 Rationale for ETV in the Treatment of Chronic HBV Infection. 13

3 NONCLINICAL DEVELOPMENT 14

3.1 Pharmacology 14

3.2 Pharmacokinetic and Metabolism Profiles. 15

3.3 Toxicology 16

3.3.1 General Toxicology 16

3.3.2 Genetic Toxicology 16

3.3.3 Carcinogenicity 18

3.3.4 Other Toxicology Findings 20

4 CLINICAL DEVELOPMENT PROGRAM 21

4.1 Overview of the Phase 1 Program. 21

4.2 Overview of Phase 2/3 Program 24

5 CLINICAL EFFICACY 26

5.1 Phase 2 Studies: Rationale for Dose Selection. 26

5.2 Pivotal Phase 3 Studies 28
5.2.1 Baseline Demographic and HBV Disease Characteristics 32
5.2.2 Efficacy Methodology 37
5.2.3 Efficacy Results 39
5.2.3.1 Nucleoside-Naive Patients (AI463022 and AI463027) 39
5.2.3.2 LVD-Refractory Patients (AI463026) 47
5.3 Exploratory Analyses 53
5.3.1 Subpopulation Analyses 53
5.3.2 Predictors of Response 56
5.4 Efficacy in Special Populations 59
5.4.1 Patients with HBV/HIV Co-infection 60
5.4.2 Patients with Decompensated Liver Disease 60
5.5 Summary of Efficacy Evaluation 61
6 RESISTANCE 61
6.1 In Vitro Resistance 61
6.2 Clinical Resistance 62
6.3 Summary of Resistance Evaluation 63
7 CLINICAL SAFETY 64
7.1 Safety Methodology 64
7.2 Extent of Exposure 66
7.2.1 Nucleoside-naive Patients 66
7.2.2 LVD-refractory Patients 66
7.2.3 Safety Cohort 66
7.3 General Safety 67
7.3.1 Deaths, Serious Adverse Events, and Adverse Events Associated with Discontinuation of Study Therapy 67
7.3.2 Adverse Events 68

7.3.3 Laboratory Abnormalities 71
7.4 ALT Flares and Other Hepatic Safety Issues 76
7.4.1 Nucleoside-Naive Patients 77
7.4.2 LVD-Refractory Patients 80
7.4.3 Other Hepatic Laboratory Abnormalities 82
7.5 Safety Cohort Analyses 82
7.5.1 Deaths 83
7.5.2 Monitoring for Malignant Neoplasms 83
7.5.3 Lactic Acidosis Signal Detection and Risk Assessment 86
7.6 Safety in Special Populations 87
7.6.1 Patients with HIV/HBV Coinfection (AI463038) 87
7.6.2 Patients with Decompensated Liver Disease (AI463048) 87
7.7 Summary of Safety Evaluation 88
8 PROPOSED PHARMACOVIGILANCE PLAN 88
9 BENEFIT VS RISK ASSESSMENT 90
9.1 Assessment of Risks 90
9.2 Assessment of Benefits 91
9.3 Benefit vs Risk Conclusions 93
10 REFERENCES 95
APPENDIX: ETV PHASE 2/3 CLINICAL STUDIES 97

LIST OF TABLES

Table 1: Summary of Week 48 Efficacy Data, Pivotal Phase 3 Studies 10
Table 3.3.2: Summary of Genetic Toxicology Data with ETV 17
Table 4.1A: Clinical Pharmacology Studies 21
Table 4.1B: Steady State PK Parameters in Healthy Subjects or Subjects with HBV Following Daily Oral 0.5 mg and 1.0 mg ETV 22
Table 4.1C: Recommended Dosage of ETV in Patients with Renal Impairment 24
Table 5.2A: Pivotal Phase 3 Studies. 28
Table 5.2B Eligibility Criteria, Pivotal Phase 3 Studies 30
Table 5.2C: Response Definitions (Week 48) 32
Table 5.2.1A: Demographic Characteristics 34
Table 5.2.1B: Baseline Histology. 35
Table 5.2.1C: Other Baseline HBV Disease Characteristics. 36
Table 5.2.3.1A Summary of Selected Efficacy Endpoints at Week 48 - Nucleoside-Naive Patients 40
Table 5.2.3.1B: Proportion Achieving HBV DNA <10^3, < 10^4, 10^5 copies/mL 43
Table 5.2.3.2: LVD-Refractory Patients (AI463026) 47
Table 5.3.1A: Subgroup Analyses, Nucleoside-Naive, HBeAg-Positive Patients (AI463022). 54
Table 5.3.1B Subgroup Analyses, Nucleoside-Naive, HBeAg-Negative Patients (AI463027). 54
Table 5.3.1C Subgroup Analyses, LVD-Refractory Patients (AI463026). 55
Table 5.3.2A: Week 48 Endpoints by Baseline Measurements - ETV-Treated Patients 57
Table 5.3.2B: Week 48 Endpoints by Week 24 Measurements - ETV-Treated Patients 58
Table 7.1: Safety Cohort. 65
Table 7.3.1: Summary of Safety Results. 68
Table 7.3.2A: Most Common Clinical Adverse Events (Reported for at Least 10% of Patients in Any Treatment Group) 69
Table 7.3.2B: Clinical Adverse Events of Moderate to Severe Intensity (Grade 2 to 4) Reported for at Least 2% of Patients in Any Treatment Group 69
Table 7.3.3A: Selected Treatment-Emergent Laboratory Abnormalities 71
Table 7.3.3B: Hematologic Abnormalities (On-Treatment) 72
Table 7.3.3C: Liver Function Test Abnormalities (On-Treatment) 73
Table 7.3.3D: Renal Function Test Abnormalities (On-Treatment) 74
Table 7.3.3E: Pancreatic Enzyme Abnormalities (On-Treatment) 75
Table 7.3.3F: Fasting Glucose Abnormalities (On-Treatment). 76
Table 7.4.1: ALT Flares - Nucleoside-Naive Patients 79
Table 7.4.2: ALT Flares - LVD-Refractory Patients 81
Table 7.4.3: Selected Treatment-Emergent Hepatic Laboratory Abnormalities, Nucleoside-Naive and LVD-Refractory Patients. 82
Table 7.5.2A: Rates of Malignant Neoplasms, Safety Cohort 84
Table 7.5.2B: Malignant Neoplasms, Safety Cohort 85

LIST OF FIGURES

Figure 4.2A: ETV Phase 2/3 Clinical Development Program 25

Figure 5.1A: Dose Response in AI463005, Nucleoside-Naive Patients (HBV DNA Mean Change from Baseline by PCR Assay) 27

Figure 5.1B: Dose Response in AI463014, LVD-Refractory Patients (HBV DNA Mean Change from Baseline by PCR Assay) 27

Figure 5.2B Study Schematic, Pivotal Phase 3 Studies 31

Figure 5.2.3.1A HBV DNA Mean Level (SE) by PCR through Week 48, Nucleoside-Naive Patients . . 44

Figure 5.2.3.1B Proportion of Patients with HBV DNA < 400 Copies/mL by PCR at Week 48, Nucleoside-Naive Patients 45

Figure 5.2.3.1C Proportion of Patients with ALT Normalization at Week 48, Nucleoside-Naive Patients 45

Figure 5.2.3.2A Co-Primary Endpoints at Week 48, LVD-Refractory Patients 49

Figure 5.2.3.2B HBV DNA Mean Level (SE) by PCR through Week 48, AI4630266. 51

Figure 5.2.3.2C Proportion of Patients with HBV DNA < 400 Copies/mL by PCR at Week 48, LVD-Refractory Patients. 51

Figure 5.2.3.2D Proportion of Patients with ALT Normalization at Week 48, LVD-Refractory Patients 52

Figure 7.5.2 Malignancy Diagnosis: Distribution over Time 84

1 OVERVIEW

Chronic infection with hepatitis B virus (HBV) causes substantial worldwide morbidity and mortality. Approximately 350 to 400 million people worldwide have chronic infection with HBV,[1,2] and over one million people die each year from the resulting complications of cirrhosis and primary hepatocellular carcinoma (HCC).[3] Intrahepatic replication of the virus and the resultant immunologic inflammatory response are factors that promote disease progression. Recent data link effective antiviral suppression induced by a nucleoside analogue to a reduced risk of hepatic decompensation and HCC.[4]

Entecavir (ETV) represents a therapeutic advance for the treatment of chronic HBV infection based on the following findings:

- Superiority of ETV over lamivudine (LVD) for histologic, virologic, and biochemical endpoints
- Low potential for development of HBV substitutions conferring viral resistance
- Low rate of associated hepatic flares

New Drug Applications (NDA 21-797 tablet; NDA 21-798 oral solution) for ETV were submitted to the United States (US) Food and Drug Administration (FDA) on 29-Sep-2004. The overall clinical benefit of ETV provided the rationale for a priority review, which was granted by the FDA on 26-Oct-2004.

ETV is an orally administered guanosine nucleoside analogue with potent and selective activity against HBV polymerase. The intracellular phosphorylation of ETV is efficient and results in an active triphosphate, ETV-TP, that inhibits all three activities of the HBV polymerase: (1) priming, (2) reverse transcription, and (3) positive strand DNA synthesis. The antiviral activity of ETV is selective for HBV, with minimal *in vitro* activity against other DNA viruses or against human immunodeficiency virus (HIV). In culture systems utilizing human liver cells that constitutively produce HBV virions, ETV demonstrates potent activity against HBV. The concentration of ETV that inhibits 50% of HBV DNA synthesis (EC_{50}) is 4 nM for wild-type (WT) HBV.[5] ETV also inhibits the replication of LVD-resistant (LVD^R) HBV, but at 8-fold higher concentrations than for the WT virus; the absolute potency of ETV against LVD^R virus in this model remains greater than that of either LVD or adefovir (ADV).[5] Additional studies in other *in vitro* cell culture

systems demonstrate that ETV is > 300-fold more potent than other HBV inhibitors that are either approved or under development (eg, LVD, ADV, telbivudine [L-deoxythymidine; LdT], or tenofovir [TDF]).[5]

The antiviral efficacy of ETV was established in standard HBV animal models: the woodchuck model using woodchuck hepatitis virus (WHV) and the duckling model using duck hepatitis B virus (DHBV). Studies in both models consistently demonstrated rapid and marked reductions (range 4 to 8 $\log_{10}$ copies/mL) in serum hepatitis virus levels at exposures relevant to those evaluated for clinical use in humans. In long-term studies of infected woodchucks, ETV maintained plasma viral DNA at undetectable levels for up to 3 years, and no resistant viral variants or changes in the viral polymerase gene were detected. Treatment with ETV delayed or prevented the onset of HCC, thereby extending the lifespan of the infected animals compared with historical data from untreated infected controls.[6] Long-term treatment with ETV was well tolerated in woodchucks.

In 2-year rodent studies, lifetime administration of ETV resulted in increased incidences of tumors relative to control animals. Two distinct patterns of tumor events were observed. Lung tumors in mice were observed at steady state exposures to ETV that represent low multiples of human exposure (≥ 3 times the human exposure). Lung tumor incidences increased with increasing dose in males, whereas in females increased incidences of lung tumors were only observed at the highest ETV exposure tested. Other tumors in rodents occurred at increased incidences relative to control animals only at the highest ETV exposures evaluated (ie, in mice, exposures equivalent to ≥ 40 times the human exposure; in rats, exposures equivalent to ≥ 24 times the human exposure).

The results of an extensive investigation of potential mechanisms for ETV rodent tumorigenesis suggest that mouse lung tumors result from a species-specific toxicity that predisposes this tissue, in which tumors occur at a high spontaneous rate in naive mice, to tumor development. Other tumors occurring at high doses/exposures in rodents are not associated with preneoplastic changes and are unlikely to result from DNA reactivity, DNA incorporation, or altered immune function. Available evidence suggests that these other tumors result when high concentrations of ETV perturb the normal balance of intracellular deoxyribonucleotide triphosphate (dNTP) pools. This effect, which is known to impair DNA synthesis and repair, is associated with a biological threshold that

must be exceeded to perturb the normal homeostatic regulation of dNTP synthesis and utilization.

ETV is a rodent carcinogen, and the investigative data do not definitively eliminate a risk to humans. The postmarketing pharmacovigilance plan for ETV includes a large simple safety study that is designed to continue the assessment of the benefit and risk of ETV.

Phase 1 studies of ETV demonstrated a favorable pharmacokinetic (PK), metabolic, and safety profile. Results of Phase 2 studies confirmed the activity of ETV against HBV and demonstrated a dose-response relationship. Pivotal Phase 3 studies investigated ETV in three HBV patient populations: nucleoside-naive hepatitis B e antigen (HBeAg)-positive patients (AI463022), nucleoside-naive HBeAg-negative patients (AI463027), and LVD-refractory HBeAg-positive patients (AI463026). Additional studies provided experience with ETV in patients who were co-infected with HIV (AI463038) or who had decompensated cirrhosis (AI463048).

Among antiviral agents assessed for anti-HBV efficacy, the development program for ETV is the first to provide comparative data using an active comparator (LVD) in nucleoside-naive patients. In LVD-refractory patients, switching to ETV was compared with continued LVD. The primary efficacy endpoint for the three Phase 3 pivotal studies was Histologic Improvement at Week 48. Virologic endpoints were assessed quantitatively by both branched DNA hybridization (bDNA) and polymerase chain reaction (PCR) assays. Other secondary endpoints include HBeAg loss, hepatitis B e (HBe) seroconversion, and alanine aminotransferase (ALT) normalization (≤ 1 × upper limit of normal [ULN]). ETV was superior to LVD for histologic and virologic endpoints in both nucleoside-naive and LVD-refractory patients (Table 1) as well as most other secondary endpoints.

Table 1: Summary of Week 48 Efficacy Data, Pivotal Phase 3 Studies

Efficacy Endpoint Study (N)	ETV	LVD	p-value
Proportion of patients who achieved Histologic Improvement			
AI463022 (ETV 314; LVD 314)	72%	62%	< 0.01
AI463027 (ETV 296; LVD 287)	70%	61%	< 0.05
AI463026 (ETV 124; LVD 116)	55%	28%	< 0.0001
Mean change from baseline in HBV DNA (log_{10} copies/mL) by PCR assay			
AI463022 (ETV 354: LVD 355)	-6.86	-5.39	< 0.0001
AI463027 (ETV 325; LVD 313)	-5.04	-4.53	< 0.0001
AI463026 (ETV 141; LVD 145)	-5.11	-0.48	< 0.0001
Proportion of patients who achieved HBV <400 copies/mL by PCR assay			
AI463022 (ETV 354: LVD 355)	69%	38%	< 0.0001
AI463027 (ETV 325; LVD 313)	91%	73%	< 0.0001
AI463026 (ETV 141; LVD 145)	21%	1%	< 0.0001

AI463022 = nucleoside-naive, HBeAg-positive patients; AI463027 = nucleoside-naive, HBeAg-negative patients; AI463026 = LVD-refractory, HBeAg-positive patients

Patients meeting study-defined response criteria were withdrawn from HBV treatment at Week 52 and were followed off-treatment for 24 weeks to assess for a sustained response and safety. The observed rates of a sustained response over 6 months of off-treatment follow-up for ETV compared favorably with those for LVD (ETV 82% vs LVD 73% in nucleoside-naive, HBeAg-positive patients).

ETV treatment did not result in the emergence of viral resistance in any of the >530 nucleoside-naive, ETV-treated patients whose Week 48 isolates were assessed. Since LVD-resistance substitutions predispose to the development of substitutions associated with ETV resistance, LVD-refractory patients are at a higher risk of developing genotypic resistance to ETV than nucleoside-naive patients. However, only 1% (2/183) of treated, LVD-refractory patients demonstrated virologic rebound due to resistance emergence within the first year of treatment.

The safety profile for ETV relative to LVD was characterized in a population of 1720 treated patients (862 ETV; 858 LVD), including all patients who received treatment in

the pivotal Phase 3 studies and a subset (ETV 1.0 mg and continued LVD groups) of those from the Phase 2 dose-ranging study in LVD-refractory patients (AI463014). Analyses were performed separately for nucleoside-naïve and LVD-refractory patients. ETV was well tolerated and had a safety profile that was comparable to that for LVD. The ETV safety profile was consistent across nucleoside-naive and LVD-refractory populations and across ETV doses (ETV 0.5 mg and 1.0 mg). ETV was associated with a low rate of ALT flares, whether assessed on- or post-treatment (≤ 6%).

Safety assessments for infrequent events were performed across a larger cohort (the Safety Cohort) that included 2399 treated patients (ETV 1392; LVD 899; placebo [PBO] 108, of whom 105 later received open-label ETV in rollover studies) from 10 Phase 2/3 studies. For both the ETV and LVD groups, the observation period for the surveillance of new diagnoses of neoplasms extends beyond the period of drug treatment. ETV and LVD demonstrated comparable patient event rates for malignancy, whether assessed per 1000 patient years (PY) of observation or as a percentage of patients exposed. The observed rates fall within the expected range for malignancies based on epidemiologic studies in populations with chronic HBV infection.

ETV is an important treatment advance that expands therapeutic options for patients with chronic HBV infection, and it provides a definable clinical benefit that outweighs the theoretical risk presented by the rodent tumor findings. The proposed indication for ETV is the treatment of chronic HBV infection in adults with evidence of active liver inflammation. The recommended dose of ETV is 0.5 mg once daily (QD) for nucleoside-naive patients and 1.0 mg QD for LVD-refractory patients.

2 INTRODUCTION AND THERAPEUTIC RATIONALE

2.1 Target Disease and Currently Available Treatment Options

Chronic infection with HBV remains a major health problem worldwide. The natural history of HBV disease is complex, as primary infection with this DNA virus results in lifelong latency even when the acute period of viral replication is self-limited. Chronic infection develops at rates ranging from < 10%, when primary infection occurs in adults, up to 90% for newborns who are infected perinatally; the risk for chronicity varies

according to the maturity of the immune system at the time of primary infection.[7] Despite the availability of an effective vaccine, chronic HBV infection remains the cause of substantial morbidity and mortality worldwide. Factors contributing to the persistent burden of HBV disease include limited healthcare resources, the inherent endemicity of HBV in certain geographic areas, and the failure to recognize and reach at-risk populations with vaccination programs. Increasing international migration means that treatment for those with established chronic HBV infection remains an important healthcare priority in regions with large numbers of immigrants, including the US.

Although the pathogenesis of HBV-related liver injury is complex, it is known that chronic intrahepatic replication of HBV results in an ongoing cascade of inflammation, injury, and repair. Without resolution, this inflammatory cycle leads to scarring and fibrosis - ending in cirrhosis and loss of hepatic function - and to uncontrolled hepatocyte regeneration with the potential for HCC. The lifetime risk for cirrhosis in those with chronic HBV infection is 40%, and cirrhosis evolves at a rate of approximately 2% per year.[8] Compensated cirrhosis is associated with a one-year survival rate over 90%.[9,10] However, compensated cirrhosis progresses to decompensation at a rate of 10% per year, and decompensation reduces the one-year survival rate to 60%.[9]

Recent data confirm that the single factor that most influences the future outcome of disease progression is the ongoing intrahepatic replication of the virus, which promotes chronic hepatic inflammation. A direct link between antiviral therapy and clinical outcome was recently demonstrated in a study that compared active treatment with LVD versus PBO in patients who had compensated cirrhosis.[4] During a median study observation period of 34 months, fewer LVD-treated patients developed either hepatic decompensation (8% LVD versus 18% PBO) or HCC (4% LVD versus 7% PBO).[11] Agents that have greater antiviral efficacy than LVD, such as ETV, would be expected to have even greater benefit.

Currently available drugs for the treatment of chronic HBV infection fall into two categories. Recombinant α interferons (α-IFNs) act primarily as endogenous immunomodulatory agents and have secondary intrinsic antiviral effects. Anti-HBV nucleoside/nucleotide analogues are antivirals that directly inhibit viral replication; both LVD and ADV inhibit HIV as well as HBV. Each treatment has characteristics that limit

its clinical usefulness in individual patients. α-IFN is administered by injection, is frequently associated with fever, flu-like symptoms, neutropenia, and depression, and is contraindicated in patients with decompensated liver function.[12] LVD is well tolerated, is available worldwide, and has been a gold standard for HBV therapy; but its long-term efficacy is limited by resistance, which develops at a rate of approximately 20% per year.[13] ADV has a favorable resistance profile (2.5% resistance after 2 years of therapy),[14] but the dose has been restricted by nephrotoxicity. At the recommended dose of 10 mg QD, ADV reduces HBV DNA by a mean of 3.6 to 4.1 $\log_{10}$ copies/mL over 48 weeks, depending on the population evaluated.[15] While providing clinical benefit, such HBV DNA decreases are modest in the context of a disease that is often associated with viral loads of 10^7 to 10^9 copies/mL.

2.2 Rationale for ETV in the Treatment of Chronic HBV Infection

The treatment of chronic HBV infection continues to present a clinical challenge. There is a need both for individual drugs and for treatment strategies that will be more effective and more durable than the current options. ETV is a cyclopentyl guanosine analogue. It is a potent and selective inhibitor of HBV replication, with activity derived from inhibition of all three enzymatic functions of the HBV polymerase. Studies on the mode of action of ETV demonstrate that in addition to competing directly with deoxyguanosine, the natural substrate for the HBV polymerase, ETV-TP is a pseudo-terminator of HBV DNA elongation.

Nonclinical data that supported the development of ETV for the treatment of chronic HBV infection included *in vitro* cell based assays demonstrating selectivity for HBV and a low EC_{50} (4 nM) for WT HBV. Although the susceptibility of LVD^R HBV to ETV is decreased relative to WT, this reduction in sensitivity can be overcome at clinically relevant concentrations of ETV. In each of two relevant animal models (woodchucks chronically infected with WHV and ducks infected with DHBV), ETV significantly reduced both plasma viral DNA (by 4 to 8 $\log_{10}$) and covalently closed circular (ccc) DNA. The cccDNA represents a genomic intermediate of HBV DNA; it serves as an intrahepatic reservoir of virus, maintaining latency and acting as a potential source for recrudescent virus when therapy is discontinued.[16,17] Long-term studies in woodchucks

demonstrated that ETV maintained plasma viral DNA at undetectable levels by PCR for up to 3 years; this was associated with clearance of cccDNA, a delay in or prevention of the onset of HCC, and an increased lifespan compared with historical data from untreated infected controls.[6] Among treated animals, 80% survived to age 4 years, compared with a historical 4-year survival rate of only 4% among untreated infected animals. While early death in infected woodchucks is primarily due to HCC, none of the ETV-treated animals sacrificed at the end of the study had histologic evidence of HCC.[6]

The nonclinical evaluation of ETV provided data from *in vitro* assays and from *in vivo* animal models suggesting that ETV would have the potential for clinical efficacy in both nucleoside-naive and LVD-refractory patients.

3 NONCLINICAL DEVELOPMENT

The nonclinical evaluation of ETV established its antiviral potency and mode of action against HBV, as well as PK and metabolic profiles, general and safety pharmacology, and toxicokinetic and toxicology profiles.

3.1 Pharmacology

The key nonclinical pharmacology findings are summarized below:

- ETV, a cyclopentyl guanosine analogue, is a potent and selective inhibitor of HBV replication
- ETV inhibits all three enzymatic functions of the viral polymerase (priming, reverse transcription, and DNA-dependent DNA synthesis)
- The EC_{50} value for ETV is 4 nM for WT HBV, compared with 1200 nM for LVD, 2400 nM for ADV, and 2300 nM for LdT
- In cell culture systems, ETV inhibits the replication of LVD^R HBV, but at 8-fold higher concentrations than for the WT virus; the absolute potency of ETV against LVD^R virus in this model remains greater than that of ADV
- ETV is efficiently phosphorylated to the active triphosphate form (ETV-TP)
- At extracellular concentrations representative of plasma levels in ETV-treated patients, intracellular ETV-TP accumulates to levels of approximately 100 nM, which would be expected to inhibit the enzymatic activity of the LVD^R HBV polymerase

- There is no *in vitro* evidence of cross-resistance between ADV and ETV,[18,19] nor of any functional interference between ETV and other nucleoside/nucleotide analogues used for the treatment of either HBV or HIV
- ETV is a poor substrate for cellular polymerases and acts as a pseudo chain terminator
  - When assayed *in vitro* using cultured cells, limited incorporation of ETV into human DNA is observed with polymerases α, β, δ, and ε; however, chain termination occurs within the next 5 bases and no full length functional DNA containing incorporated ETV can be identified
  - In the same *in vitro* system, there is no detectable ETV incorporated into DNA by human mitochondrial polymerase γ
- Using *in vitro* polymerase assays, ETV-TP inhibits the human, woodchuck, and duck HBV polymerases more effectively than LVD-triphosphate (LVD-TP)
- In WHV-infected woodchucks, long-term (14 or 36 months) oral administration of ETV is effective and well tolerated based on the following findings:
  - Administration of ETV 0.5 mg/kg (exposure comparable to a 1.0-mg human dose) suppresses viral replication during 3 years of treatment
  - Survival rates at 4 years of age for WHV-infected woodchucks treated for 14 or 36 months are 50% and 80%, respectively, compared with 4% for historical controls ($p = 0.00002$ for the 14- and 36-month combined treatment groups)
  - The incidence of HCC in WHV-infected woodchucks is markedly reduced
  - There is no evidence of ETV resistance in the WHV polymerase gene after up to 3 years of treatment
- ETV is >1,000-fold more potent than LVD in DHBV-infected hepatocytes, has superior efficacy, and is well tolerated in a duckling model using DHBV infection

3.2 Pharmacokinetic and Metabolism Profiles

Key nonclinical PK and metabolism findings are summarized below:

- ETV is highly bioavailable in various animal species and humans although it has lower bioavailability in cynomolgus monkeys
- The steady state volume of distribution of ETV in animals is greater than the volume of total body water, suggesting extensive extravascular distribution of the drug
- Low serum protein binding is demonstrated in all species
- ETV is not a substrate, inhibitor, or inducer of cytochrome (CYP) isozymes
- In rats, dogs, cynomolgus monkeys, and humans, ETV is metabolized only to a minor extent via conjugation of parent drug (also known as Phase II metabolism), resulting

in the formation of glucuronide and sulfate metabolites; all metabolites that are observed in human plasma are also detected in rat, dog, and cynomolgus monkey plasma

- The primary route for elimination of ETV is renal excretion, with parent drug as the major form present in urine
- In rats, cynomolgus monkeys, and humans, the rate of renal clearance is greater than the glomerular filtration rate (GFR), indicating that renal elimination occurs via a combination of glomerular filtration and net tubular secretion
- ETV is not a substrate of human P-glycoprotein (P-gp); thus, ETV is unlikely to interact with drugs that are transported by P-gp

3.3 Toxicology

3.3.1 General Toxicology

In single-dose oral studies in rodents, ETV was well tolerated at doses up to 200 mg/kg.

The major findings in subchronic or chronic oral toxicology studies conducted in mice, rats, dogs, and cynomolgus monkeys were as follows:

- In 6-month studies in mice, lung changes consisting of alveolar histiocytosis, bronchioloalveolar hyperplasia, and benign adenomas were noted at exposures to ETV ≥ 29 times those in humans
- In 6-month studies in mice and rats, liver degeneration was observed at all the doses tested
- In 3-month studies in dogs, reversible perivascular inflammation in the central nervous system (CNS) was observed; both no-effect and threshold doses were established for this finding; at these doses, exposures to ETV were 23- and 90-fold higher, respectively, than in humans at the 0.5-mg dose (13- and 51-fold higher than at the 1.0-mg dose in humans)
- In a 1-year study in cynomolgus monkeys, ETV was well tolerated, with no drug-related toxicity in any organ, including target organs noted above in mice, rats, and dogs; in this study, systemic exposure to ETV was 242 times that in humans at 0.5 mg (or 136 times at 1.0 mg)

3.3.2 Genetic Toxicology

The genotoxic potential of ETV was evaluated in a battery of *in vitro* and *in vivo* test systems (Table 3.3.2).

- ETV was clastogenic in human lymphocytes at high, cytotoxic concentrations (≥ 36 μM; about 10,000 times higher than the concentration of ETV that inhibited 50% of viral DNA synthesis in cultured human liver HepG2 cells)
- ETV did not induce micronuclei formation in an *in vivo* micronucleus study in rats, even at toxic dosages
- ETV was negative in other *in vitro* and *in vivo* assays, including an *in vivo-in vitro* hepatocyte DNA repair study in rats
- The weight of evidence from a battery of genetic toxicology studies supports the conclusion that ETV is not DNA-reactive

The clastogenicity finding was not unexpected because *in vitro* clastogenicity is a class effect for nucleoside analogues. However, other clastogenic guanosine analogues such as ganciclovir and penciclovir are also positive for induction of micronuclei *in vivo*, thereby corroborating the *in vitro* clastogenicity findings whereas ETV was not positive in this test. In cell culture, ETV perturbed the normal balance of dNTP pools at concentrations associated with clastogenicity; thus, dNTP pool perturbations may be the mechanism by which ETV was clastogenic in human lymphocytes.

Table 3.3.2: Summary of Genetic Toxicology Data with ETV

Test	Result	NOEL or LOEL[a]	Exposure Multiple[b]
Ames (*Salmonella* and *Escherichia coli*) Assay	Negative	5000 μg/plate	NA[c]
CHO/HGPRT Assay	Negative	1000 μg/ml	NA[c]
SHE-Cell Transformation Assay	Negative	2 μg/ml	NA[c]
Clastogenicity Assay (human lymphocytes)	Positive	10 μg/ml	NA[c]
In Vivo Micronucleus Study (rat bone marrow)	Negative	2000 mg/kg	>2240
In Vivo/In Vitro Unscheduled DNA Synthesis (UDS) Study	Negative	2000 mg/kg	>2240

[Note] With the exception of the Ames assay, ETV was tested up to cytotoxic concentrations/doses; the Ames assay was tested up to the maximum concentration recommended internationally

[a] No observed effect level (NOEL) or lowest observed effect level (LOEL) for genotoxicity

[b] Exposure multiple relative to that in humans at 1.0 mg

[c] Not applicable

3.3.3 Carcinogenicity

The carcinogenic potential of ETV was evaluated in lifetime studies conducted in mice and rats. Key observations from these studies are as follows:

- In male mice, ETV increased the incidence of lung tumors at low exposure multiples (3 and 5 times the ETV exposure in humans at the 1.0-mg and 0.5-mg doses, respectively). The incidence of these tumors increased in a dose-related manner. The incidence of lung tumors was also increased in female mice at the highest dose tested (4 mg/kg); at this dose, exposure to ETV was 40 and 70 times higher than in humans at the 1.0- and 0.5-mg doses, respectively.
- In mice, ETV increased incidences of tumors in organs other than the lung (liver in male mice; vascular system and salivary gland in female mice) at the highest dose tested (4 mg/kg; exposures to ETV ≥ 70 times the human exposure at the 0.5-mg dose and ≥ 40 times at the 1.0-mg dose).
- In rats, ETV increased incidences of tumors in rats (brain gliomas and renal tumors in males; gliomas and liver tumors in females) at the highest doses tested (1.4 and 2.6 mg/kg in males and females, respectively. Exposures to ETV at these doses were ≥ 43 times the human exposure at the 0.5-mg dose and ≥ 24 times at the 1.0-mg dose.

ETV-induced lung tumors in mice are distinguished from all other tumor findings by the exposure multiples at which they occurred and by the observation of early preneoplastic changes. Investigative studies were conducted to evaluate the mode of action underlying the development of these tumors, and the key observations from these studies were as follows:

- ETV treatment causes early histopathological changes in the mouse lung manifested as increased numbers of macrophages and Type II pneumocytes in the alveolar region.
- The increase in macrophages results from recruitment of these cells into the lung by a direct chemotactic effect of ETV. The macrophages are not activated, and the macrophage is the only inflammatory cell that accumulates in the lung.
- The increase in Type II pneumocytes results from sustained proliferation of these cells.
- Macrophage recruitment is linked to and required for proliferation of Type II pneumocytes. Mice lacking chemokine receptor 2 (CCR2) showed a delayed response to the effects of ETV in the lung. In this model, there was no increase in proliferation of Type II pneumocytes until an increased number of macrophages was observed.

- Type II pneumocytes are the major progenitor cell in the alveolar epithelium and mouse lung tumors typically arise from these cells. ETV-induced lung tumors were shown to arise from the proliferating Type II pneumocytes.
- The effects of ETV in mouse lung were species-specific, as no drug-related pulmonary changes were observed in rats, dogs, or cynomolgus monkeys.
- ETV was chemotactic to mouse but not human monocytes, suggesting that macrophage accumulation, a critical event in the etiology of ETV-induced mouse lung tumors, is unlikely to occur in humans.
- The widely-used anti-oxidant, butylated hydroxytoluene (BHT), increases lung tumor development in a species-specific manner (mice only) with macrophage-supported Type II cell proliferation as a key step in tumor development.

All other ETV-induced tumors in rodents were distinguished from mouse lung tumors by the higher multiples of exposure associated with tumor development and the lack of preneoplastic lesions or other relevant histopathological changes in the affected tissues. Based on the genetic toxicology data, these tumors were not considered to result from a direct interaction with DNA or inappropriate incorporation of ETV into DNA. Furthermore, there was no evidence that any of the observed tumors result from immunotoxicity or immunosuppression.

A possible mode of action underlying the development of the high dose tumors may involve perturbation of stable dNTPs pool sizes, which are essential for the maintenance of the fidelity of DNA synthesis and repair. This mode of action is also consistent with a high-dose, threshold effect because it would require high concentrations of drug to overcome the normal, tightly regulated homeostatic mechanisms involved in regulating dNTP pools. Investigative studies, conducted to determine whether ETV induced dNTP pool perturbations, indicated the following:

- At a carcinogenic dose in mice (4 mg/kg; ≥ 40 times human exposure at the 1.0-mg dose), ETV significantly decreased the dGTP pool in mouse liver with a concurrent increase in hepatic dATP concentrations. The net effect was a marked perturbation in the total hepatic content of purine dNTPs.
- At the highest non-carcinogenic dosage of ETV in mice (0.4 mg/kg; ≥ 10 times human exposure at the 1.0-mg dose), ETV decreased hepatic dGTP, but to a lesser extent than at the high dose, and there was no concomitant change in any other dNTP, particularly dATP.
- ETV-induced dNTP pool perturbations is a plausible mode of action to explain rodent tumor development at high ETV exposures.

ETV is a rodent carcinogen, and the investigative data submitted to the FDA Carcinogenicity Assessment Committee (CAC) do not definitively eliminate a risk to humans.

3.3.4 Other Toxicology Findings

Reproductive and Developmental Toxicology

- In reproductive and developmental toxicity studies in rats, ETV demonstrates no selective developmental toxicity, no effects on reproductive function or fertility, and no adverse findings in a perinatal/postnatal study at exposures ≥ 28 times that in humans at 1.0 mg/day
- ETV is a selective (embryo-fetal) developmental toxicant in rabbits; however, at the no-effect dose, exposure to ETV is approximately 210 times higher than in humans at 1.0 mg/day

Assessment of Mitochondrial Risk

- In a primer extension assay, ETV does not inhibit mitochondrial DNA polymerase γ ; moreover, incorporation of ETV into the DNA products of polymerase γ is undetectable at concentrations as high as 160 μM
- ETV has little effect on mitochondrial DNA synthesis in HepG2 cells
- ETV has no effect on oxidative metabolism in HepG2 cells at exposures that do not affect overall cell viability
- Overall, these data indicate that ETV has little or no potential for mitochondrial toxicity

Cardiovascular Safety Pharmacology

- ETV does not demonstrate any cardiovascular effects on action potential parameters (rabbit and canine Purkinje fibers) or potassium and calcium channel currents that are attributable to the drug at ETV concentrations up to 30 μM (approximately 1000 times higher than the maximum observed concentration [Cmax] in humans administered ETV 1.0 mg/day)
- In repeat-dose studies in dogs and cynomolgus monkeys, no evidence of drug-related electrocardiogram (ECG) effects is observed at ETV exposures ≥ 136 times the human exposure at therapeutic doses

4 CLINICAL DEVELOPMENT PROGRAM

4.1 Overview of the Phase 1 Program

The Phase 1 clinical pharmacology program evaluated the PK and safety of ETV in 19 studies conducted in healthy subjects (Table 4.1A). In addition, a retrospective analysis of ECG data (AI463041) from five Phase 1 studies (AI463001, AI463002, AI463010, AI463033, and AI463034) was performed. Furthermore, a population PK analysis was performed (AI463017) using data from three Phase 2 studies (AI463004, AI463005 and AI463014). Another Phase 2 study assessed the PK of ETV when co-administered with either cyclosporine or tacrolimus in OLT recipients (AI463015).

Table 4.1A: Clinical Pharmacology Studies

Type of Study	Number of Subjects	Study Number(s)
Single ascending-dose	88	AI463001, AI463021
Multiple ascending dose	84	AI463002, AI463029, AI463033
Combined single ascending and multiple ascending-dose	68	AI463018
Absorption, Distribution, Metabolism and Excretion	6	AI463031
Drug interactions[a]	131	AI463010, AI463058, AI463063, AI463066
Age-gender	52	AI463042
Renal impairment	34	AI463011
Hepatic impairment	32	AI463032
Bioequivalence	94	AI463034, AI463035, AI463065
Food effect	55	AI463003, AI463016
Total number of subjects evaluated in ETV clinical pharmacology studies	**644**	

[a] Drugs evaluated for interaction included LVD (AI463010 and AI463058), ADV (AI463063), and TDF (AI463066).

Note: In addition, a retrospective analysis of ECG data (AI463041) from five studies (AI463001, AI463002, AI463010, AI463033, and AI463034) and a population PK/pharmacodynamic (PD) analysis (AI463017) for selected Phase 2 studies (AI463004, AI463005, and AI463014) were performed.

The key findings of the clinical pharmacology studies are summarized below:

Biopharmaceutics

- A single 1.0-mg ETV tablet is bioequivalent to two 0.5-mg tablets
- ETV 0.5-mg oral solution is bioequivalent to a single 0.5-mg tablet
- ETV AUC is decreased by approximately 20% when administered with food

PK Profile

- The PK profile of ETV in HBV-infected patients is similar to that in healthy subjects (Table 4.1B)

Table 4.1B: Steady State PK Parameters in Healthy Subjects or Subjects with HBV Following Daily Oral 0.5 mg and 1.0 mg ETV

	Tmax (h) Median (Min, Max)	Cmax (ng/mL) Mean (SD)	Cmin (ng/mL) Mean (SD)	AUC(TAU) (ng•h/mL) Mean (SD)	CLT/F (mL/min) Mean (SD)
ETV 0.5 mg					
Healthy Subjects (N = 12)	0.88 (0.5, 1.0)	5.49 (1.9)	0.3 (0.05)	16.4 (2.4)	520.7 (94.7)
HBV Subjects[a] (N = 75)	NA[b]	4.17 (1.13)	0.53 (0.32)	21.3 (9.03)	442.0 (138.1)
ETV 1.0 mg					
Healthy Subjects (N = 11)	0.75 (0.5, 1.5)	10.15 (2.8)	0.48 (0.07)	31.60 (5.4)	543.2 (102.8)
HBV Subjects[a] (N = 29)	NA[b]	9.70 (3.3)	1.36 (1.03)	53.9 (28.8)	384.9 (168.9)

[a] Values for the HBV subjects are estimates based on Population PK modeling and simulation.

[b] Tmax was set at 0.5 hours in the population PK model

Absorption

- Following oral administration in healthy subjects, ETV is rapidly absorbed, with peak plasma concentrations occurring between 0.5 and 1.5 hours
- ETV exhibits approximately 2-fold accumulation, and steady state is achieved approximately 6 to 10 days following the start of QD administration
- The effective accumulation half-life of ETV is approximately 24 hours, supporting QD administration

Distribution

- ETV is extensively distributed in tissues and has an apparent volume of distribution greater than total body water
- Mean protein binding is 13%

Metabolism

- ETV is not a substrate, inhibitor, or inducer of the cytochrome P450 enzymes
- ETV is metabolized via conjugation of the parent drug, resulting in the production of small amounts of glucuronide (plasma) and sulfate (feces) metabolites (≤ 10% of dose)

Elimination

- ETV is predominantly eliminated by the kidney, with urinary recovery of unchanged drug at steady state ranging from 62% to 73% of the administered dose
- Renal clearance is independent of dose and ranges from 360 to 471 mL/min, indicating that ETV undergoes both glomerular filtration and net tubular secretion

Dose Adjustment

- No dose adjustments are recommended based on age, gender, or race
- The PK profile of hepatically impaired patients is similar to that of healthy control subjects
- Moderate and severe renal impairment results in higher drug exposure
- Mean steady state ETV exposures in OLT recipients are higher than the steady state ETV exposure in healthy subjects when both groups are given the 1.0-mg/day dose; Altered renal function in the OLT recipients accounts for most of this difference
- There are no plasma PK drug-drug interactions between ETV and LVD, ADV, or TDF

Recommendations for dose adjustment for patients with moderate to severe renal impairment are presented in Table 4.1C.

Table 4.1C: Recommended Dosage of ETV in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Usual Dose (0.5 mg)	Lamivudine Refractory (1.0 mg)
≥50	0.5 mg QD	1.0 mg QD
30 to <50	0.25 mg QD	0.5 mg QD
10 to <30	0.15 mg QD	0.3 mg QD
Hemodialysis or CAPD[a]	0.1 mg QD	0.2 mg QD

[a] Administer after hemodialysis

Potential Effects on Electrocardiograms

Both *in vitro* and *in vivo* nonclinical studies indicated that ETV has a low potential for prolongation of QT or PR intervals (Section 3.3.4). Electrocardiographic observations in humans including both healthy volunteers and patients with chronic HBV infection, are summarized below:

- In a retrospective analysis of ECGs in 187 healthy volunteers enrolled in five Phase 1 studies (three of which included a PBO control), there was no evidence of treatment-related prolongation of the QTcB or QTcF interval from baseline
- In a Phase 2 dose-escalating study in 34 ETV-treated patients with chronic HBV infection (doses ranging from 0.05 to 1.0 mg/day), there was no evidence of treatment-related ECG abnormalities

4.2 Overview of Phase 2/3 Program

An extensive Phase 2/3 clinical development program assessed the efficacy and safety of ETV in the treatment of chronic HBV infection (Figure 4.2A). Many of these studies remain ongoing. Results from 12 studies provide data supporting the efficacy and safety of ETV. These results include Week 48 treatment data and 6-month off-treatment follow-up data for three large Phase 3 studies and early analyses for supportive studies.

The Phase 2/3 clinical studies are listed in the appendix.

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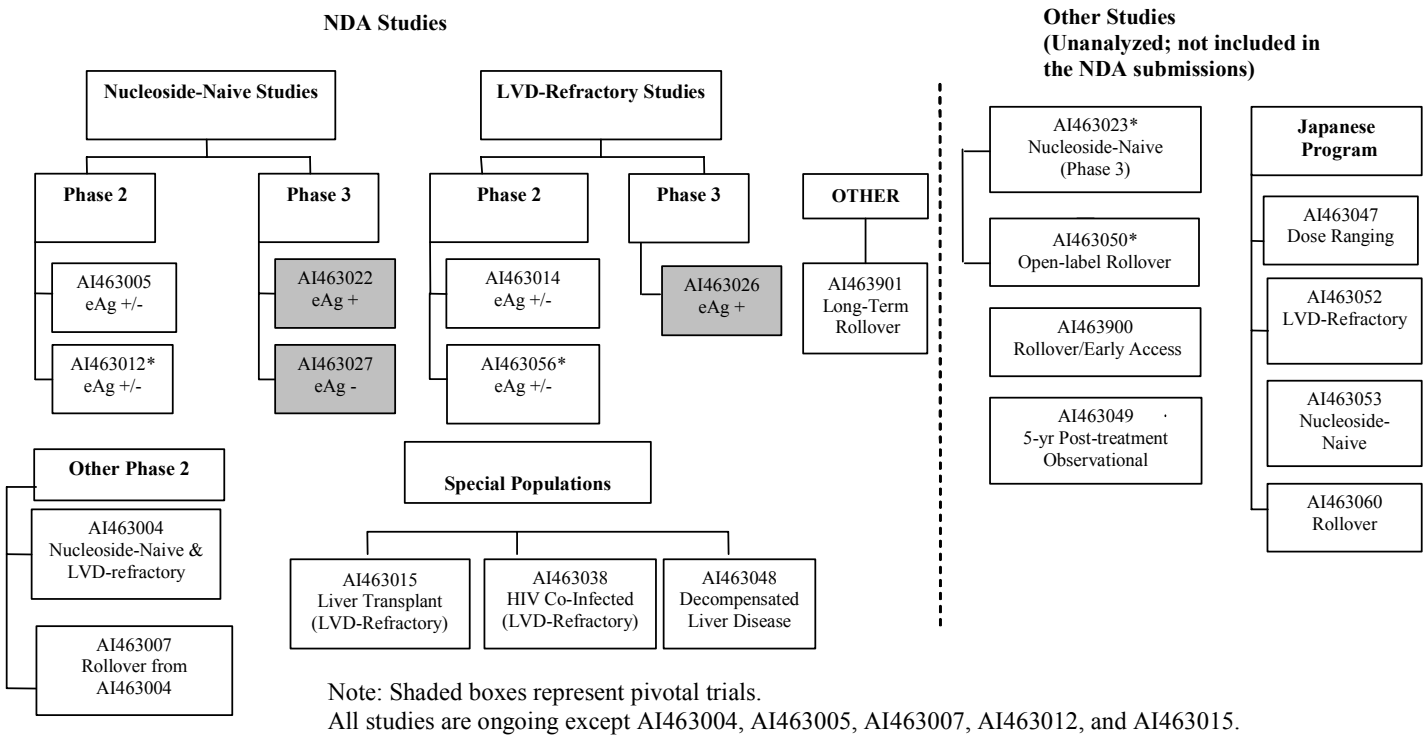
Figure 4.2A: ETV Phase 2/3 Clinical Development Program



Note: Shaded boxes represent pivotal trials.
All studies are ongoing except AI463004, AI463005, AI463007, AI463012, and AI463015.
* Chinese Programs

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5 CLINICAL EFFICACY

5.1 Phase 2 Studies: Rationale for Dose Selection

The early efficacy evaluation of ETV was based on assessments of quantitative HBV DNA reduction in Phase 2 dose-ranging studies. The dose selection for the Phase 3 studies was based on results from two Phase 2 dose-ranging studies. The 22-week study in nucleoside-naive patients (AI463005) demonstrated that ETV 0.1 mg and 0.5 mg showed superior HBV DNA reduction compared with LVD at Week 22 (Figure 5.1A). The 48-week study in LVD-refractory patients (AI463014) demonstrated that ETV 1.0 mg was superior to lower doses of ETV (0.1 mg and 0.5 mg) in HBV DNA reduction at Week 24 (Figure 5.1B). A dose-response relationship was demonstrated across the doses of ETV. ETV 1.0 mg also demonstrated greater and more consistent antiviral activity compared with the lower doses of ETV or LVD over 48 weeks of treatment, making it the most appropriate dose for LVD-refractory patients. Thus, the highest dose evaluated for each patient population in these Phase 2 studies was selected for the Phase 3 evaluation of ETV: 0.5 mg in nucleoside-naive patients and 1.0 mg in LVD-refractory patients.

Figure 5.1A: Dose Response in AI463005, Nucleoside-Naive Patients (HBV DNA Mean Change from Baseline by PCR Assay)

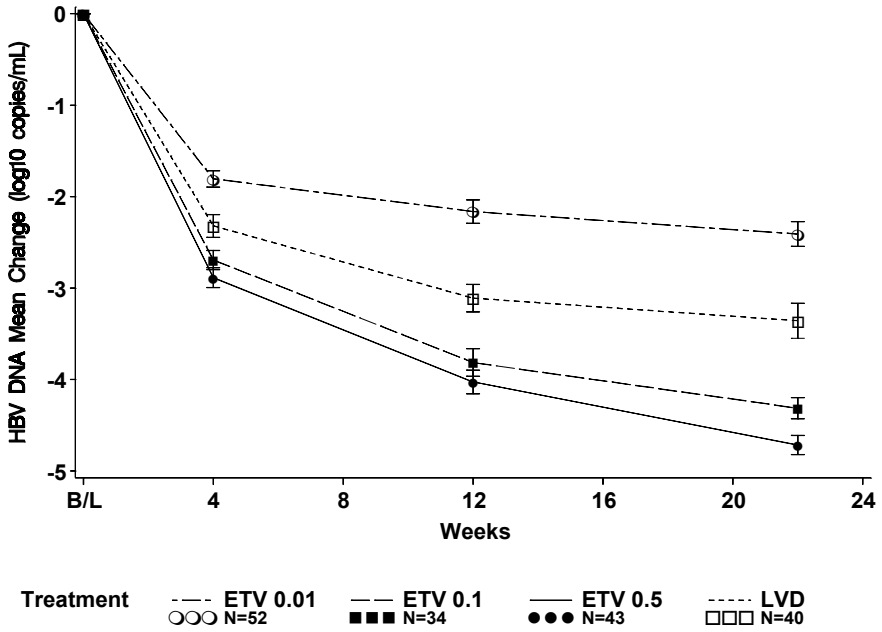
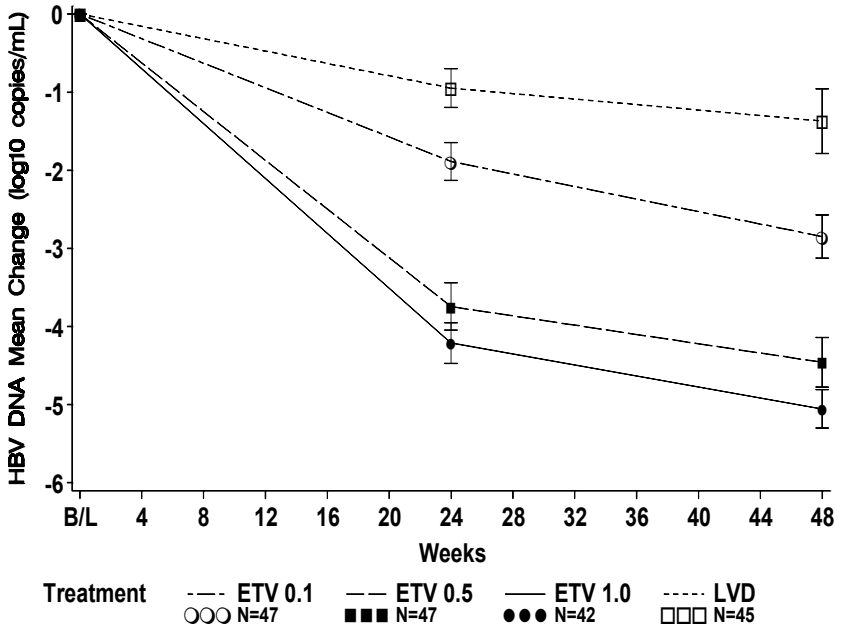


Figure 5.1B: Dose Response in AI463014, LVD-Refractory Patients (HBV DNA Mean Change from Baseline by PCR Assay)



5.2 Pivotal Phase 3 Studies

The efficacy of ETV was assessed in three large, multinational, randomized, double-blind Phase 3 studies (Table 5.2A)

Table 5.2A: Pivotal Phase 3 Studies

Protocol	Study Population	Treatment (PO, QD)	Number of Patients Treated
NUCLEOSIDE-NAIVE PATIENTS[a]			
AI463022	HBeAg+	ETV 0.5 mg	354
		LVD 100 mg	355
AI463027	HBeAg– /HBeAb+	ETV 0.5 mg	325
		LVD 100 mg	313
LVD-REFRACTORY PATIENTS[b]			
AI463026	HBeAg+ incomplete response to LVD	ETV 1.0 mg	141
		LVD 100 mg	145
TOTAL		**ETV**	**820**
		LVD	**813**
TOTAL - ALL POPULATIONS			**1633**

[a] Patients who had ≤ 12 weeks of prior nucleosides/nucleotide exposure

[b] Patients with viremia while on LVD (HBV DNA ≥ 0.7 MEq/mL by bDNA assay; or approximately ≥ 10^5 $\log_{10}$ copies/mL) or with evidence of LVD^R substitutions

The two studies in the nucleoside-naive population were designed to characterize the efficacy of ETV in the treatment of patients with either HBeAg-positive (AI463022) or HBeAg-negative (presumed precore mutant, AI463027) disease, thus addressing the two most important disease patterns among nucleoside-naive patients. The other study (AI463026) evaluated the use of ETV in HBeAg-positive patients with LVD-refractory HBV infection, a population that is emerging as increasingly important and whose treatment options are limited by viral resistance.

Treatment with LVD provided an active comparator group in all three studies. In both studies of nucleoside-naive patients, ETV 0.5 mg QD was compared with LVD 100 mg QD, while in the study of LVD-refractory patients, ETV 1.0 mg QD was compared with continued LVD 100 mg QD. For the study in LVD-refractory patients, continuing

treatment with LVD represented the best available treatment option at the time the study was designed and initiated. The clinical practice of continuing LVD in this patient population was supported by observations suggesting that, for at least some period after the identification of LVD^R virus, this approach maintained lower HBV DNA and lower ALT levels than the only clinical alternative, which was to discontinue therapy.

Evidence of compensated liver function and active hepatic inflammation were required for entry into all three studies. Eligibility criteria for the pivotal Phase 3 studies are presented in Table 5.2B. Efficacy endpoints were assessed across four standard parameters: histology, virology, biochemical assays, and serology. A uniform study design was used in the pivotal Phase 3 studies and is presented as a general schematic in Figure 5.2B.

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Table 5.2B Eligibility Criteria, Pivotal Phase 3 Studies

Eligibility criteria	Nucleoside-Naïve AI463022	Nucleoside-Naïve AI463027	LVD-Refractory AI463026
Males and females ≥ 16 years with history of chronic hepatitis B infection	+	+	+
HBV viremia			
• HBV DNA ≥ 0.7 MEq/mL by bDNA *or* > 1.5 million copies/mL by PCR ≥ 4 weeks prior to screening	+	–	+
• HBV DNA ≥ 0.7 MEq/mL by bDNA *or* > 100,000 copies/mL by PCR ≥ 2 weeks prior to screening	–	+	–
• HBV DNA ≥ 3.0 MEq/mL by bDNA at screening	+	–	+
• HBV DNA ≥ 0.7 MEq/mL by bDNA at screening	–	+	–
• HBV DNA ≥ 10 MEq/mL by bDNA at screening	–	–	–
HBV serology			
• Detectable HBsAg ≥ 6 months or detectable HBsAg < 6 months *and* negative for IgM core antibody *and* confirmation of chronic hepatitis on liver biopsy	+	+	+
• HBeAg positive at screening and at least once ≥ 4 weeks prior to screening	+	–	+
• HBeAg negative/anti-HBeAb positive at screening and at least once ≥ 4 weeks prior to screening	–	+	–
• HBeAg could be positive or negative at screening	–	–	–
ALT			
• ALT 1.3 to 10 x ULN at screening and at least once ≥ 12 weeks prior to screening	+	+	+
• ALT and AST normal to ≤ 10 x ULN at screening	–	–	–
Liver biopsy			
• Evidence of chronic hepatitis on liver biopsy performed ≤ 52 weeks prior to randomization	+	+	+
Previous LVD therapy			
• LVD treatment ≥ 24 weeks (in AI463014) or ≥ 36 weeks (in AI463026) <u>or</u> documented YMDD mutation regardless of the duration of therapy	–	–	+

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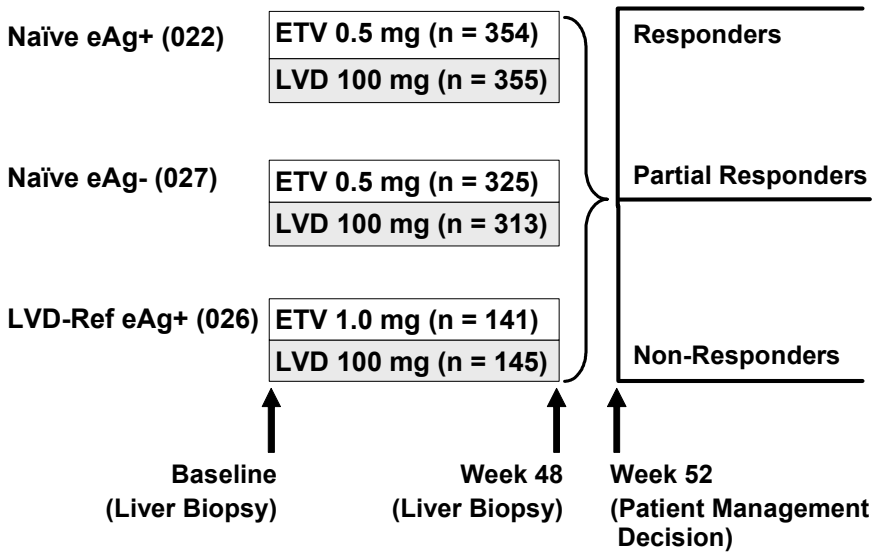
Figure 5.2B Study Schematic, Pivotal Phase 3 Studies



All three studies provided at least 52 weeks of blinded treatment. Efficacy parameters were assessed at Week 48 and results for all serum-based secondary efficacy parameters were available to investigators at Week 52, permitting a clinical assessment of response to therapy at that visit. Patient management for the second year of the study was based on the Week 48 response (Table 5.2C) according to a protocol-specified management algorithm that had been designed to reflect clinical practice.

Patients classified as responders met study-specified criteria for response at Week 48, using a definition appropriate to their HBeAg status; responders were withdrawn from study therapy and were observed for an additional 24 weeks in order to assess both off-treatment safety and sustained response. Partial responders at Week 48 (virologic response only, by bDNA assay) continued for a second year of blinded treatment through Week 96. Non-responders could rollover to a long-term treatment study or could seek the best available alternate therapy outside the ETV program. All patients who stopped ETV therapy, regardless of the time or reason for discontinuation, were followed for 24 weeks in the post-treatment follow-up period for safety monitoring.

Table 5.2C: Response Definitions (Week 48)

Term	Definition	Study
Response	HBV DNA < 0.7 MEq/mL by bDNA *and* loss of HBeAg	AI463022 AI463026
	HBV DNA < 0.7 MEq/mL by bDNA *and* ALT < 1.25 x ULN	AI463027
Partial response	HBV DNA < 0.7 MEq/mL by bDNA *but* HBeAg-positive	AI463022 AI463026
	HBV DNA < 0.7 MEq/mL by bDNA *but* ALT ≥ 1.25 x ULN	AI463027
Non-response	HBV DNA ≥ 0.7 MEq/mL by bDNA	AI463022 AI463026 AI463027

5.2.1 Baseline Demographic and HBV Disease Characteristics

Demographic Characteristics

Baseline demographic characteristics for treated patients were consistent with those expected for populations with chronic HBV infection (Table 5.2.1A). Within each of the three Phase 3 studies, the ETV and LVD groups were balanced for baseline demographic characteristics. In all three studies, approximately 75% of patients were male. The majority of nucleoside-naive, HBeAg-positive patients were Asian, and Asia contributed the largest number of patients in this study. The majority of nucleoside-naive, HBeAg-negative patients and of LVD-refractory patients were White, and Europe contributed the largest numbers of patients in these studies. Among nucleoside-naive patients, the mean age of HBeAg-negative patients was approximately 10 years older than that of HBeAg-positive patients, consistent with the biology and disease pattern of HBeAg-negative HBV infection.

Baseline HBV Disease Characteristics

Treatment groups were balanced for baseline histology within each of the three Phase 3 studies (Table 5.2.1B). As anticipated, the mean Knodell necroinflammatory score was lower in LVD-refractory patients than in nucleoside-naive patients. Among nucleoside-naive patients, the distribution of baseline fibrosis scores for HBeAg-negative patients is shifted toward greater severity compared with the distribution for

HBeAg-positive patients. This finding is consistent with the biology of HBeAg-negative disease. Consistent with the entry requirement for compensated liver function, only a small proportion of patients had evidence of cirrhosis by either the Knodell or Ishak scoring system.

Non-histology baseline HBV-disease characteristics are presented in Table 5.2.1C. As would be expected in HBeAg-negative patients, baseline HBV DNA levels were approximately 2 $\log_{10}$ lower than in HBeAg-positive patients. In the LVD-refractory population, 85% of patients had evidence of LVD resistance mutations by Ino-Lipa assay at baseline.

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Table 5.2.1A: Demographic Characteristics

	Nucleoside-Naïve				LVD-Refractory	
	AI463022 HBeAg +		AI463027 HBeAg -		AI463026 HBeAg +	
	ETV 0.5 mg N = 354	LVD 100 mg N = 355	ETV 0.5 mg N = 325	LVD 100 mg N = 313	ETV 1.0 mg N = 141	LVD 100 mg N = 145
Age (Years)						
Mean (se)	35 (0.7)	35 (0.7)	44 (0.6)	44 (0.6)	39 (1.2)	39 (1.1)
SD	13	13	11	11	15	14
Median	33	32	45	45	38	40
Min, Max	16, 76	16, 78	18, 76	18, 77	16, 74	17, 70
Missing	0	0	0	0	0	0
Gender: N (%)						
Male	274 (77)	261 (74)	248 (76)	236 (75)	105 (74)	112 (77)
Female	80 (23)	94 (26)	77 (24)	77 (25)	36 (26)	33 (23)
Race: N (%)						
Asian[a]	204 (58)	202 (57)	122 (38)	129 (41)	57 (40)	50 (34)
White	140 (40)	141 (40)	193 (59)	176 (56)	83 (59)	93 (64)
Other	10 (3)	12 (3)	10 (3)	8 (3)	1 (<1)	2 (1)
Region: N (%)						
Asia	172 (49)	167 (47)	106 (33)	104 (33)	35 (25)	36 (25)
Europe	84 (24)	88 (25)	156 (48)	148 (47)	62 (44)	72 (50)
North America	47 (13)	55 (15)	28 (9)	27 (9)	31 (22)	24 (17)
South America	51 (14)	45 (13)	35 (11)	34 (11)	13 (9)	13 (9)

[a] Includes native Hawaiian/other Pacific Islander

Note: Percentages are based on patients with measurements.

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Table 5.2.1B: Baseline Histology

	Nucleoside-Naïve				LVD-Refractory	
	AI463022		AI463027		AI463026	
	ETV 0.5 mg N = 354	LVD 100 mg N = 355	ETV 0.5 mg N = 325	LVD 100 mg N = 313	ETV 1.0 mg N = 141	LVD 100 mg N = 145
Knodell necroinflammatory score, mean (SE)[a]	7.8 (0.16)	7.7 (0.16)	8.0 (0.16)	7.7 (0.16)	6.5 (0.28)	6.5 (0.30)
Knodell necroinflammatory score ≥ 2, N (%)	314 (89)	314 (88)	296 (91)	287 (92)	124 (88)	116 (80)
Ishak fibrosis score, mean (SE)	2.3 (0.07)	2.3 (0.07)	2.4 (0.07)	2.5 (0.08)	2.3 (0.13)	2.2 (0.12)
Knodell fibrosis score	**(N = 341)**	**(N = 340)**	**(N = 315)**	**(N = 308)**	**(N = 141)**	**(N = 140)**
0 = None	8 (2)	7 (2)	6 (2)	2 (<1)	7 (5)	10 (7)
1 = Portal	209 (61)	216 (64)	167 (53)	171 (56)	81 (57)	71 (51)
3 = Bridging	87 (26)	80 (24)	111 (35)	92 (30)	33 (23)	44 (31)
4 = Cirrhosis	25 (7)	27 (8)	19 (6)	28 (9)	14 (10)	9 (6)
99 = Inadequate specimen	12 (4)	10 (3)	12 (4)	15 (5)	6 (4)	6 (4)
Ishak fibrosis score						
0 = No fibrosis	8 (2)	7 (2)	6 (2)	2 (<1)	7 (5)	10 (7)
1 = Fibrous, some portal areas	77 (23)	88 (26)	58 (18)	56 (18)	37 (26)	35 (25)
2 = Fibrous, most portal areas	132 (39)	128 (38)	109 (35)	115 (37)	43 (30)	36 (26)
3 = Fibrous, most portal areas with occasional bridging	66 (19)	60 (18)	79 (25)	63 (20)	25 (18)	32 (23)
4 = Fibrous, all portal areas + marked bridging	21 (6)	21 (6)	35 (11)	29 (9)	9 (6)	12 (9)
5 = Marked bridging with occasional nodules (incomplete cirrhosis)	14 (4)	15 (4)	11 (3)	18 (6)	5 (4)	4 (3)
6 = Cirrhosis, probable or definite	11 (3)	11 (3)	5 (2)	10 (3)	9 (6)	5 (4)
99 = Inadequate specimen	12 (4)	10 (3)	12 (4)	15 (5)	6 (4)	6 (4)

[a] Data are limited to patients with evaluable baseline histology. AI463022: ETV 314, LVD 314; AI463027: ETV 296, LVD 287; AI463026: ETV N = 124; LVD N = 116

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Table 5.2.1C: Other Baseline HBV Disease Characteristics

	Nucleoside-Naïve				LVD-Refractory	
	AI463022		AI463027		AI463026	
	ETV 0.5 mg N = 354	LVD 100 mg N = 355	ETV 0.5 mg N = 325	LVD 100 mg N = 313	ETV 1.0 mg N = 141	LVD 100 mg N = 145
HBV DNA by bDNA (log_{10} MEq/mL)mean (SE)	2.56 (0.06)[a]	2.61 (0.05)	1.24 (0.05)	1.23 (0.06)	2.50 (0.08)	2.50 (0.08)
HBV DNA by PCR (log_{10} copies/mL) mean (SE)	9.62 (0.11)	9.69 (0.11)	7.61 (0.10)	7.55 (0.10)	9.48 (0.15)	9.24 (0.13)
LVD-R mutation, N (%)	NA	NA	NA	NA	118 (84)	124 (86)
Hepatitis B surface antigen , N (%)						
Positive	354 (100)	355 (100)	325 (100)	312 (>99)	141 (100)	145 (100)
Negative	0	0	0	1 (<1)	0	0
Hepatitis B e antigen, N (%)						
Positive	348 (98)	351 (99)	2 (<1) [b]	4 (1) [b]	136 (96)	142 (98)
Negative	6 (2)[c]	4 (1) [c]	322 (99)	309 (99)	5 (4) [c]	3 (2) [c]
Hepatitis B e antibody, N (%)						
Negative	342 (97)	346 (97)	2 (<1)	1 (<1)	135 (96)	140 (97)
Positive	12 (3)	9 (3)	323 (99)	312 (>99)	6 (4)	5 (3)
ALT (U/L), mean (SE)	140.5 (6.08)	146.3 (7.03)	141.0 (6.36)	142.5 (6.75)	123.9 (9.2)	131.9 (13.8)

[a] 1 log_{10} MEq/mL is equivalent to 6 log_{10} copies/mL.

[b] Patients reverted to HBeAg-positive between screening and Day 1 (baseline).

[c] Patients converted to HBeAg-negative between screening and Day 1 (baseline).

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5.2.2 Efficacy Methodology

Primary Endpoint

The proportion of patients with Histologic Improvement was a primary measure of efficacy in all three Phase 3 studies. All liver biopsy specimens were evaluated by a single independent central biopsy reader (Zachary D. Goodman, MD, PhD) in sequence-blinded and treatment-blinded pairs (baseline and Week 48). Histologic Improvement was defined as a ≥ 2-point decrease from baseline in the Knodell necroinflammatory score[20] with no worsening of fibrosis (worsening was defined as a ≥ 1-point increase from baseline in the Knodell fibrosis score) at the Week 48 liver biopsy. This specific definition was based on precedent established by previous HBV efficacy trials, and as for other nucleoside antivirals, the histologic benefit has been assessed while on therapy at Week 48. Within a 48-week timeframe, the necroinflammatory component generally drives the histologic response regardless of the antiviral used, as would be expected given the pathophysiology of HBV-related liver disease.

Change in histology of the liver is a challenging endpoint which directly reflects the clinical status of the end-organ that results in HBV disease morbidity and mortality. Histology also represents a downstream consequence, one that follows the immediate antiviral-induced reduction in HBV replication. Withdrawal of the inflammatory stimulus (virus) leads to a subsequent decrease in the inflammatory response in the liver (measured histologically by necroinflammation) associated with a stabilization in fibrosis. Actual improvement in fibrosis would only be expected to occur with prolonged resolution of the inflammatory process. The question of whether histologic scoring will be sensitive enough to distinguish between two active antiviral regimens[21] has been answered by the ETV clinical data. These data were the first to provide a direct comparison of histologic outcomes between two active antiviral regimens, and results show that superiority is demonstrable in the setting of differing antiviral potency.

Analyses of histologic endpoints were performed using the population of patients who had evaluable baseline histology (eg, those whose baseline biopsy had a Knodell necroinflammatory score ≥ 2, and who therefore had the possibility of achieving Histologic Improvement at Week 48). Those having missing or inadequate biopsies at

Week 48 were assessed as failures (Non-Completer = Failure [NC = F]). The primary histology endpoint was assessed in two steps for both nucleoside-naive studies. The difference (ETV - LVD) was tested first for non-inferiority, and then for superiority only if the former criterion was met. A boundary of -10% was prespecified for comparison with the lower limit of the 95% confidence interval for non-inferiority; this -10% boundary is consistent with current conventions for antiviral studies.

For LVD-refractory patients, there was no precedent of a controlled trial assessing histologic change with either ongoing LVD or with an alternate nucleoside. Therefore, the estimates of response rates used in the power calculations to establish the size of the study were based on case series reports. Moreover, it was anticipated that patients continuing to receive LVD might have lower Knodell necroinflammatory scores at baseline compared with nucleoside-naive patients, which could reduce the ability to demonstrate a treatment difference over 48 weeks. This led to a design using two independent, co-primary endpoints for the Phase 3 study in LVD-refractory patients (AI463026). The first was Histologic Improvement (described above). The second was a composite that reflects the parameters often used to determine patient management in the routine clinical setting, which are markers of viral suppression and biochemical improvement. This Composite Endpoint assessed the proportion of patients at Week 48 who achieved an HBV DNA < 0.7 MEq/mL by bDNA assay *and* serum ALT < 1.25 × ULN. The superiority tests were performed separately for the two co-primary endpoints, and a Bonferroni adjustment was applied. ETV was considered to be superior to LVD for a co-primary endpoint if the lower limit of the 97.5% confidence interval was greater than zero.

Secondary Endpoints

Quantitative serum HBV DNA is increasingly recognized as an important measure of response to therapy in chronic HBV infection, since HBV DNA levels reflect the intrahepatic replication of virus, which causes the end-organ inflammation and disease. For the ETV program, quantitative HBV DNA was assessed using both the bDNA assay (Bayer Quantiplex™; lower limit of quantitation [LOQ] 0.7 MEq/mL) and the PCR assay (Roche COBAS Amplicor, LOQ currently recognized at 300 copies/mL). The PCR methodology provides greater sensitivity and therefore the possibility of greater differentiation between the two treatments studied. The studies incorporated the bDNA

assay into the assessment of clinical response categories and the clinical management algorithm implemented at Week 52 because the LOQ for this assay has been incorporated as a clinically meaningful endpoint in current HBV management guidelines.[7,22]

Key secondary efficacy endpoints in these Phase 3 studies included the following, organized by response category:

- Virologic Responses:
  - Mean reduction from baseline in HBV DNA by PCR assay
  - Proportion with HBV DNA < 400 copies/mL by PCR assay (and < 300 copies/mL which is the LOQ of the Roche COBAS assay)
  - Proportion with HBV DNA < 0.7 MEq/mL by bDNA assay
- Biochemical Response: proportion with normalization of ALT (≤ 1 × ULN)
- Other Histology:
  - Proportion with improvement (≥ 1 point decrease) in the Ishak fibrosis score (patients with evaluable baseline histology)
  - Subset analyses on cccDNA at Week 48 biopsy
- Serologic Response (for HBeAg-positive patients):
  - Proportion with loss of HBeAg
  - Proportion with HBe seroconversion

The principal analysis across all proportion-based endpoints, whether virologic, biochemical, or serologic, was a modified intent-to-treat (ITT) method, in which all treated patients were analyzed and those having missing measurements at Week 48 were assessed as failures (NC = F).

5.2.3 Efficacy Results

5.2.3.1 Nucleoside-Naive Patients (AI463022 and AI463027)

A summary of selected efficacy endpoints at Week 48 for nucleoside-naive patients is presented in Table 5.2.3.1A.

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Table 5.2.3.1A Summary of Selected Efficacy Endpoints at Week 48 - Nucleoside-Naive Patients

	AI463022 -HBeAg-Positive		AI463027 - HBeAg-Negative	
Selected Efficacy Endpoint	ETV 0.5 mg N = 354	LVD 100 mg N = 355	ETV 0.5 mg N = 325	LVD 100 mg N = 313
Histologic Improvement, n (%)[a,b] Primary Endpoint)	**226 (72)**	**195 (62)**	**208 (70)**	**174 (61)**
Difference Estimate (ETV-LVD) (95% CI)	**9.9 (2.6, 17.2)**		**9.6 (2.0, 17.3)**	
p-value	**p = 0.0085**		**p = 0.0143**	
Knodell Necroinflammatory Score Improvement, n (%)[a,b]	231 (74)	200 (64)	217 (73)	183 (64)
Difference Estimate (ETV-LVD) (95% CI)	9.9 (2.7, 17.1)		9.5 (2.0, 17.1)	
p-value	p = 0.0077		p = 0.0130	
Ishak Fibrosis Score Improvement, n (%)[a,b]	121 (39)	111 (35)	107 (36)	109 (38)
Difference Estimate (ETV-LVD) (95% CI)	3.2 (-4.4, 10.7)		-1.8 (-9.7, 6.0)	
p-value	p = 0.41		p = 0.65	
Hepatic cccDNA,[c] Mean Change From Baseline (SE) ($\log_{10}$ copies/HGEq)	-0.9 (0.05)	-0.7 (0.05)	-0.5 (0.05)	-0.5 (0.06)
Difference Estimate (ETV-LVD) (95% CI)	-0.2 (-0.3, -0.1)		-0.0 (-0.2, 0.1)	
p-value	p = 0.0033		p = 0.50	
HBV DNA Mean Change From Baseline (SE) by PCR[d] ($\log_{10}$ copies/mL)	-6.86 (0.108)	-5.39 (0.143)	-5.04 (0.098)	-4.53 (0.111)
Difference Estimate (ETV-LVD) (95% CI)	-1.52 (-1.78, -1.27)		-0.43 (-0.60, -0.26)	
p-value	p < 0.0001		p <0.0001	
HBV DNA < 400 copies/mL by PCR, n (%)[a]	246 (69)	135 (38)	297 (91)	230 (73)
Difference Estimate (ETV-LVD) (95% CI)	31.5 (24.5, 38.4)		17.9 (12.1, 23.7)	
p-value	p < 0.0001		p < 0.0001	

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Table 5.2.3.1A Summary of Selected Efficacy Endpoints at Week 48 - Nucleoside-Naive Patients

	AI463022 -HBeAg-Positive		AI463027 - HBeAg-Negative	
Selected Efficacy Endpoint	ETV 0.5 mg N = 354	LVD 100 mg N = 355	ETV 0.5 mg N = 325	LVD 100 mg N = 313
HBV DNA < 300 copies/mL by PCR, n (%)[a]	236 (67)	129 (36)	293 (90)	225 (72)
Difference Estimate (ETV-LVD) (95% CI)	30.3 (23.3, 37.3)		18.3 (12.3, 24.2)	
p-value	p < 0.0001		p < 0.0001	
HBV DNA < 0.7 MEq/mL by bDNA assay, n (%)[a]	322 (91)	232 (65)	309 (95)	279 (89)
Difference Estimate (ETV-LVD) (95% CI)	25.6 (19.8, 31.4)		5.9 (1.8, 10.1)	
p-value	p < 0.0001		p = 0.0053	
ALT Normalization ≤ 1 × ULN, n (%)[a]	242 (68)	213 (60)	253 (78)	222 (71)
Difference Estimate (ETV-LVD) (95% CI)	8.4 (1.3, 15.4)		6.9 (0.2, 13.7)	
p-value	p = 0.0202		p = 0.0451	
HBe Seroconversion,[a] n (%)	74 (21)	64 (18)	--	--
Difference Estimate (ETV-LVD) (95% CI)	2.9 (-2.9, 8.7)			
p-value	p = 0.33			
Sustained Response[a,e] n (%)	61 (82)	49 (73)	124 (48)	78 (35)

[a] NC = F

[b] Proportions based on number of patients with evaluable baseline histology: AI463022: ETV N = 314, LVD N = 314; AI463027: ETV N = 296, LVD N = 287

[c] AI463022: ETV N = 159, LVD N = 146; AI463027: ETV N = 107, LVD N = 104

[d] AI463022: ETV N = 340, LVD N = 324; AI463027: ETV N = 314, LVD N = 295

[e] HBV DNA < 0.7 MEq/mL *and* loss of HBeAg (AI463022): ETV N = 74, LVD N = 67; HBV DNA < 0.7 MEq/mL *and* ALT < 1.25 × ULN: (AI463027): ETV N = 259, LVD N = 220

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Primary Endpoint: Histologic Improvement

In both HBeAg-positive and HBeAg-negative nucleoside-naive populations, ETV 0.5 mg demonstrated superiority over LVD 100 mg for the primary efficacy endpoint, the proportion of patients who achieved Histologic Improvement at Week 48 (Table 5.2.3.1A). Among HBeAg-positive patients, the proportions were 72% for ETV (226/314 patients) and 62% for LVD (195/314 patients) ($p = 0.0085$). Among HBeAg-negative patients, the proportions were 70% for ETV (208/296 patients) and 61% for LVD (174/287 patients) ($p = 0.0143$).

Other Histologic Endpoints

In both HBeAg-positive and HBeAg-negative nucleoside-naive populations, ETV 0.5 mg was superior to LVD 100 mg for the proportion of patients with improvement in the Knodell necroinflammatory score at Week 48 (Table 5.2.3.1A). ETV 0.5 mg was similar (non-inferior) to LVD 100 mg for the proportion of patients with improvement in the Ishak fibrosis score (≥ 1-point decrease from baseline) at Week 48 (Table 5.2.3.1A).

Hepatic cccDNA

Hepatic cccDNA is a stable genomic repository of HBV in the nucleus of infected hepatocytes that is thought to serve as a viral reservoir, thereby maintaining latency and contributing to post-treatment reactivation of HBV replication and to clinical relapse. The Phase 3 pivotal studies provided for an exploratory assessment of paired baseline and Week 48 cccDNA. Results from 159 ETV-treated and 146 LVD-treated nucleoside-naive, HBeAg-positive patients demonstrated that ETV 0.5 mg was superior to LVD 100 mg for the mean reduction in hepatic cccDNA, with a decrease of 0.9 $\log_{10}$ copies/HGEq for ETV compared with 0.7 $\log_{10}$ copies/HGEq for LVD ($p = 0.0033$) (Table 5.2.3.1A). The HBeAg-negative, nucleoside-naive patients had a lower baseline level of cccDNA compared with the HBeAg-positive patients, which limited the ability to detect a treatment difference in the HBeAg-negative population. Results for the HBeAg-negative population demonstrated that ETV 0.5 mg was similar (non-inferior) to LVD 100 mg, with a decrease of 0.5 $\log_{10}$ copies/HGEq in each treatment group (Table 5.2.3.1A).

HBV DNA

ETV 0.5 mg was superior to LVD 100 mg for all measures of virologic response in both HBeAg-positive and HBeAg-negative nucleoside-naive populations (Table 5.2.3.1A). The absolute values of the decreases in serum HBV DNA by PCR assay at Week 48 for the ETV group were substantial: 6.9 $\log_{10}$ copies/mL in HBeAg-positive patients and 5.0 $\log_{10}$ copies/mL in HBeAg-negative patients. The higher mean baseline HBV DNA level in HBeAg-positive patients (9.6 $\log_{10}$ copies/mL) permitted ETV to demonstrate a greater reduction in HBV DNA at Week 48 compared with HBeAg-negative patients (baseline mean 7.6 $\log_{10}$ copies/mL). Conversely, the low mean baseline HBV DNA in HBeAg-negative patients resulted in a large proportion of patients achieving a Week 48 HBV DNA < 400 copies/mL, thereby limiting the ability to assess the full extent of HBV DNA reduction in this population. Mean HBV DNA levels for HBeAg-positive and HBeAg-negative patients are shown in Figure 5.2.3.1A.

The proportions of HBeAg-positive patients who achieved HBV DNA < 400 copies/mL by PCR were 69% for ETV compared with 38% for LVD. The proportions in HBeAg-negative patients were greater for ETV than for LVD (91% and 73%, respectively) (Figure 5.2.3.1B, Table 5.2.3.1A). Proportions achieving alternate levels of suppression by PCR are included in Table 5.2.3.1B, as these may be relevant for assessing ETV in relation to evolving treatment guidelines.

Table 5.2.3.1B Proportions Achieving HBV DNA < 10^3, 10^4, 10^5 copies/mL

	Number (%) of Patients			
	Nucleoside-Naive, HBeAg+		Nucleoside-Naive, HBeAg-	
HBV DNA (copies/mL)	ETV 0.5 mg N = 354	LVD 100 mg N = 355	ETV 0.5 mg N =325	LVD 100 mg N = 313
< 10^3	277 (78)	150 (42)	301 (93)	243 (78)
< 10^4	320 (90)	188 (53)	306 (94)	262 (84)
< 10^5	335 (95)	226 (64)	311 (96)	277 (88)

Figure 5.2.3.1A HBV DNA Mean Level (SE) by PCR through Week 48, Nucleoside-Naive Patients

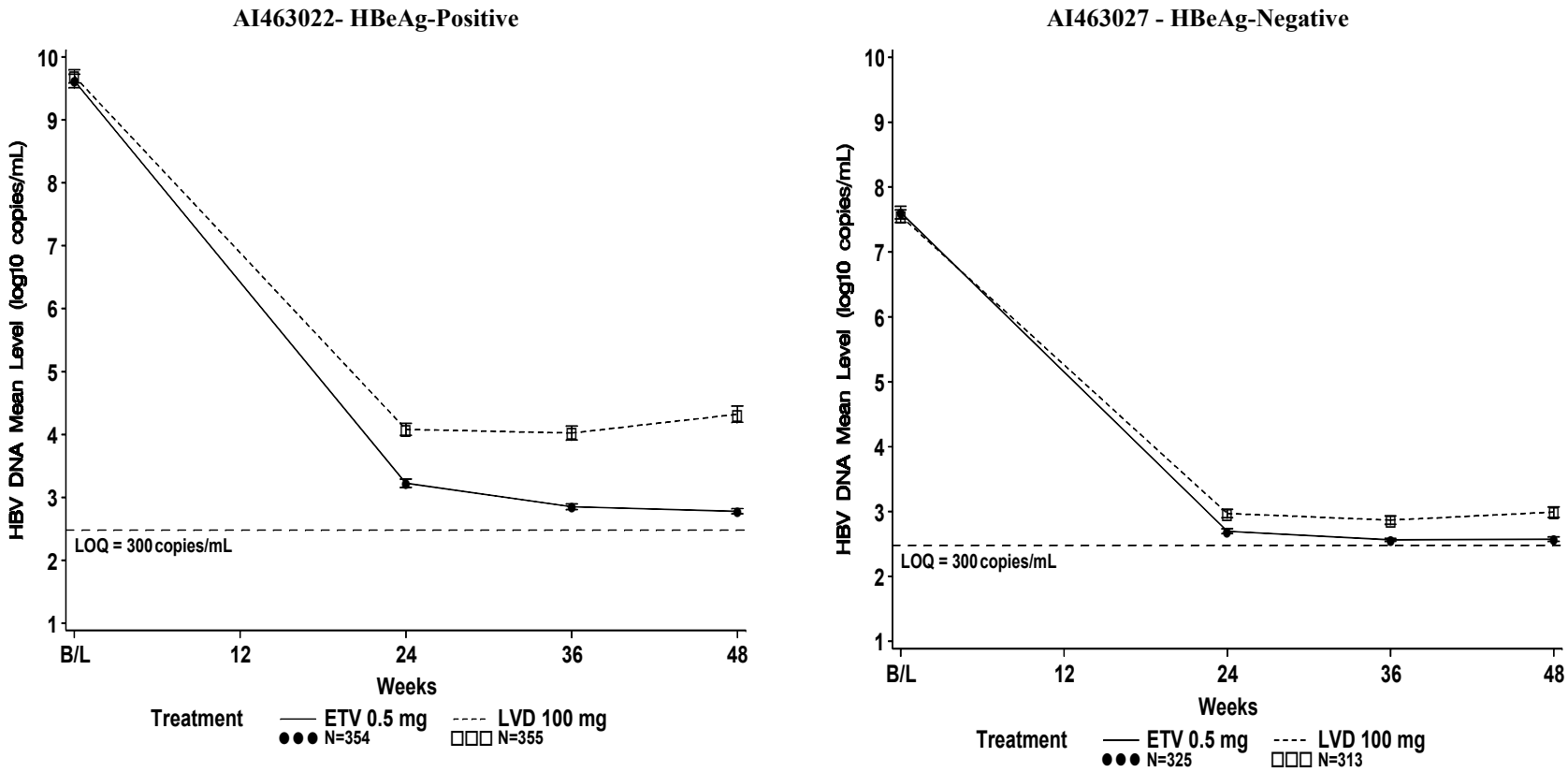

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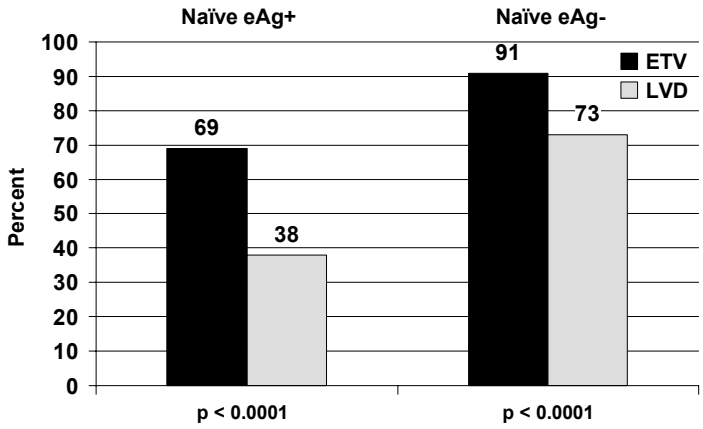
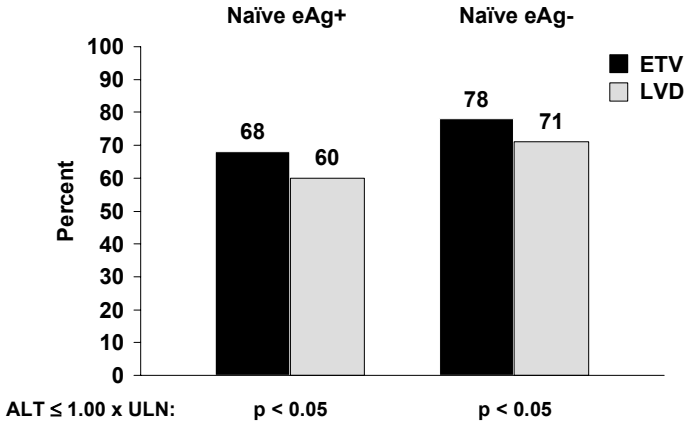
Figure 5.2.3.1B Proportion of Patients with HBV DNA < 400 Copies/mL by PCR at Week 48, Nucleoside-Naive Patients



ALT Normalization

ETV 0.5 mg was superior to LVD 100 mg for the proportion of patients who achieved ALT normalization (≤ 1 × ULN) in nucleoside-naive patients, regardless of the HBeAg status (Table 5.2.3.1A, Figure 5.2.3.1C).

Figure 5.2.3.1C Proportion of Patients with ALT Normalization at Week 48, Nucleoside-Naive Patients



Antigen Loss and Seroconversion

Among HBeAg-positive patients, ETV 0.5 mg was similar (non-inferior) to LVD 100 mg for the proportion of patients with loss of HBeAg at Week 48 (ETV 22%; LVD 20%) and for the proportion with HBe seroconversion (ETV 21%; LVD 18%) (Table 5.2.3.1A). Few individuals in either treatment group achieved loss of serum HBsAg at Week 48 regardless of HBeAg status (HBeAg-positive: ETV 6 patients, LVD 4 patients; HBeAg-negative: 1 patient in each treatment group).

Sustained Response Off Therapy

HBeAg-Positive Patients

The analysis of sustained response in nucleoside-naive, HBeAg-positive patients included those who demonstrated a combined virologic and serologic response (HBV DNA < 0.7 MEq/mL by bDNA *and* loss of HBeAg) at Week 48. This response endpoint is primarily driven by HBeAg loss, with 21% of ETV-treated patients vs 19% of LVD-treated patients achieving this endpoint at Week 48. These responders were discontinued from therapy and were followed off-treatment for an additional 24 weeks. Among eligible patients (ETV = 74; LVD = 67), the proportion of patients who sustained the response of HBV DNA < 0.7 MEq/mL by bDNA *and* loss of HBeAg at off-treatment Week 24 was 82% for ETV 0.5 mg and 73% for LVD 100 mg. Kaplan-Meier plots of the proportion with sustained response through 24 weeks off-treatment showed a separation in favor of ETV 0.5 mg that developed between Weeks 8 and 12 of the 24-week follow-up period.

HBeAg-Negative Patients

The majority of nucleoside-naive, HBeAg-negative patients in both treatment groups (ETV 274 [84%] vs LVD 244 [78%]) achieved a combined virologic and biochemical response (HBV DNA < 0.7 MEq/mL by bDNA assay *and* ALT < 1.25 × ULN) at Week 48. Because some clinicians chose to discontinue study drug beyond the Week 65 timepoint, the analysis for sustained response in HBeAg-negative patients included those responders who discontinued study therapy on or before Week 65. Among eligible patients (ETV = 259; LVD = 220), the proportion of patients who sustained the response of HBV DNA < 0.7 MEq/mL by bDNA assay *and* ALT < 1.25 × ULN at off-treatment Week 24 was 48% for ETV and 35% for LVD. Kaplan-Meier plots for this endpoint

showed the largest drop in response for LVD-treated patients around the Week 8 measurements, whereas ETV-treated patients had the largest drop in response around the Week 24 measurements. Of the ETV-treated patients, 59% had a sustained virologic response of HBV DNA < 0.7 MEq/mL by bDNA assay through 24 weeks off treatment compared with 46% of LVD-treated patients. However, when the more sensitive PCR assay was used, HBV DNA was detectable in 97% of ETV-treated patients and 96% of LVD-treated patients at off-treatment Week 24. These data suggest a need to further evaluate the appropriate duration and endpoint of treatment in the HBeAg-negative population.

5.2.3.2 LVD-Refractory Patients (AI463026)

A summary of selected efficacy endpoints at Week 48 for LVD-refractory patients is presented in Table 5.2.3.2.

Table 5.2.3.2: Summary of Selected Efficacy Endpoints at Week 48 - LVD-Refractory Patients

Selected Efficacy Endpoint	ETV 1.0 mg N = 141	LVD 100 mg N = 145
Histologic Improvement, n (%)[a,b] (Co-Primary Endpoint)	**68 (55)**	**32 (28)**
Difference Estimate (ETV-LVD) (95% CI)	**27.3 (13.6, 40.9)**	
p-value	**p < 0.0001**	
HBV DNA < 0.7 MEq/mL by bDNA and ALT < 1.25 ULN (Co-Primary Endpoint)[a]	**77 (55)**	**6 (4)**
Difference Estimate (ETV-LVD) (95% CI)	**50.5 (40.4, 60.6)**	
p-value	**p < 0.0001**	
Knodell Necroinflammatory Score Improvement,[a,b] n (%)	68 (55)	37 (32)
Difference Estimate (ETV-LVD) (95% CI)	22.9 (10.7, 35.1)	
p-value	p = 0.0003	
Ishak Fibrosis Score Improvement, n (%)[a,b]	42 (34)	19 (16)
Difference Estimate (ETV-LVD) (95% CI)	17.5 (6.8, 28.2)	
p-value	p = 0.0019	
Hepatic ccc DNA,[c] Mean Change From Baseline (SE) ($\log_{10}$ copies/HGEq)	-0.6 (0.07)	0.0 (0.09)
Difference Estimate (ETV-LVD) (95% CI)	-0.6 (-0.8, -0.4)	
p-value	p < 0.0001	
HBV DNA Mean Change (SE) From Baseline by PCR ($\log_{10}$ copies/mL)	-5.11 (0.194)	-0.48 (0.174)
Difference Estimate (ETV-LVD) (95% CI)	-4.4 (-4.8, -4.0)	
p-value	p < 0.0001	

Table 5.2.3.2: Summary of Selected Efficacy Endpoints at Week 48 - LVD-Refractory Patients

Selected Efficacy Endpoint	ETV 1.0 mg N = 141	LVD 100 mg N = 145
HBV DNA < 400 copies/mL by PCR, n (%)[d]	29 (21)	2 (1)
Difference Estimate (ETV-LVD) (95% CI)	19.2 (12.3, 26.1)	
p-value	p < 0.0001	
HBV DNA < 300 copies/mL by PCR, n (%) [a]	27 (19)	2 (1)
Difference Estimate (ETV-LVD) (95% CI)	17.8 (11.0, 24.5)	
p-value	p < 0.0001	
HBV DNA < 0.7 MEq/mL by bDNA assay, n (%)[a]	93 (66)	8 (6)
Difference Estimate (ETV-LVD) (95% CI)	60.4 (51.8, 69.1)	
p-value	p < 0.0001	
ALT Normalization ≤ 1 × ULN[a]	86 (61)	22 (15)
Difference Estimate (ETV-LVD) (95% CI)	45.8 (35.9, 55.8)	
p-value	p < 0.0001	
HBe Seroconversion[a] n (%)	11 (8)	4 (3)
Difference Estimate (ETV-LVD) (95% CI)	5.0 (-0.1, 10.2)	
p-value	p = 0.06	
Sustained Response,[e] n/N	5/13	1/1

[a] NC = F

[b] Proportions were calculated based on the number of patients with evaluable baseline histology. ETV N = 124, LVD N = 116

[c] ETV N = 74, LVD N = 59

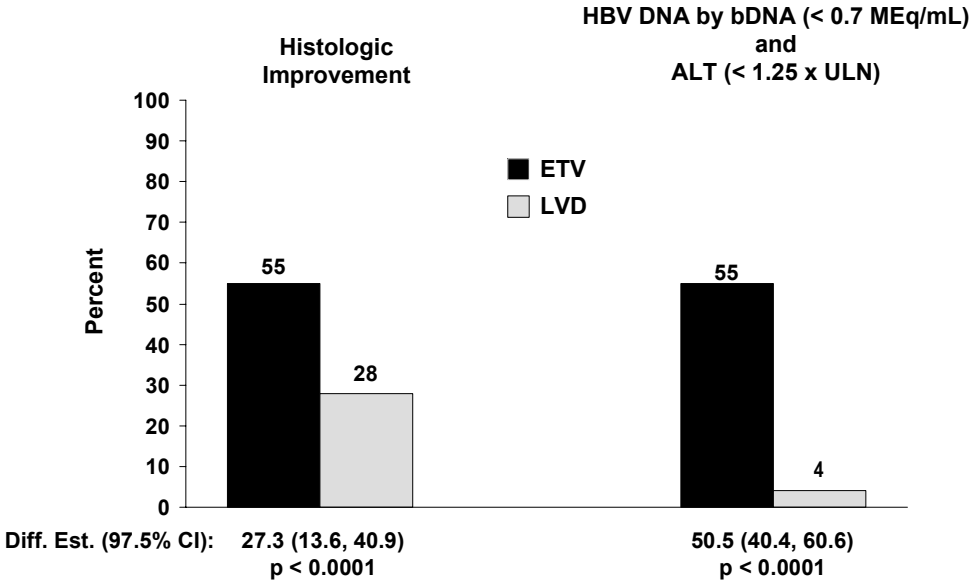
[d] ETV N = 133, LVD N = 128

[e] HBV DNA < 0.7 MEq/mL *and* loss of HBeAg

Co-Primary Endpoints: Histologic Improvement and Composite Endpoint

ETV 1.0 mg was superior to continued LVD 100 mg at Week 48 as assessed by both co-primary endpoints (Figure 5.2.3.2A, Table 5.2.3.2). The proportions of patients who achieved Histologic Improvement were 55% (68/124) for ETV and 28% for LVD (32/116) ($p < 0.0001$). The proportion of patients who achieved the Composite Endpoint were 55% (77/141) for ETV and 4% (6/145) for LVD ($p < 0.0001$).

Figure 5.2.3.2A Co-Primary Endpoints at Week 48, LVD-Refractory Patients



Other Histologic Endpoints

The superiority of ETV 1.0 mg to continued LVD 100 mg was demonstrated in the proportion of patients who achieved improvement in Knodell necroinflammatory score (ETV 55% vs LVD 32%; p = 0.0003) and Ishak fibrosis score (ETV 34% vs LVD 16%; p = 0.0019) at Week 48 (Table 5.2.3.2). Furthermore, fewer patients in the ETV 1.0-mg group had worsening of fibrosis compared with patients in the LVD 100-mg group (ETV 11% [14/124] vs LVD 26% [30/116]) as assessed by the Ishak fibrosis score.

Hepatic cccDNA

For this exploratory analysis in LVD-refractory patients, ETV 1.0 mg was superior to continued LVD 100 mg for the reduction of hepatic cccDNA assessed in paired baseline and Week 48 liver biopsy samples. The mean reductions were 0.6 $\log_{10}$ copies/HGEq for ETV compared with 0.0 $\log_{10}$ copies/HGEq for continued LVD ($p < 0.0001$) (Table 5.2.3.2).

HBV DNA

ETV 1.0 mg was superior to continued LVD 100 mg for all measures of virologic response (Table 5.2.3.2). The mean reduction in HBV DNA by PCR at Week 48 was 5.1 $\log_{10}$ copies/mL for ETV 1.0 mg compared with 0.5 $\log_{10}$ copies/mL for continued LVD 100 mg. Mean HBV DNA levels are presented in Figure 5.2.3.2B. When assessing the consistency of response to ETV across the Phase 3 studies, the lower mean HBV DNA reduction (5.1 vs 6.9 $\log_{10}$ copies/mL) and the lower proportion achieving an HBV DNA < 400 copies/mL (21% vs 69%) in LVD-refractory patients compared with nucleoside-naive HBeAg-positive patients, are both consistent with the higher EC_{50} of LVD^R virus.

A greater proportions of patients in the ETV group than in the LVD group achieved an HBV DNA < 400 copies/mL by PCR assay: ETV 21% vs LVD 1% (Figure 5.2.3.2C, Table 5.2.3.2). Moreover, 66% of ETV-treated patients compared with 6% of LVD-treated patients achieved an HBV DNA < 0.7 MEq/mL by bDNA assay, a meaningful cutoff that has been integrated into clinical guidelines.[7]

Figure 5.2.3.2B HBV DNA Mean Level (SE) by PCR through Week 48, AI463026

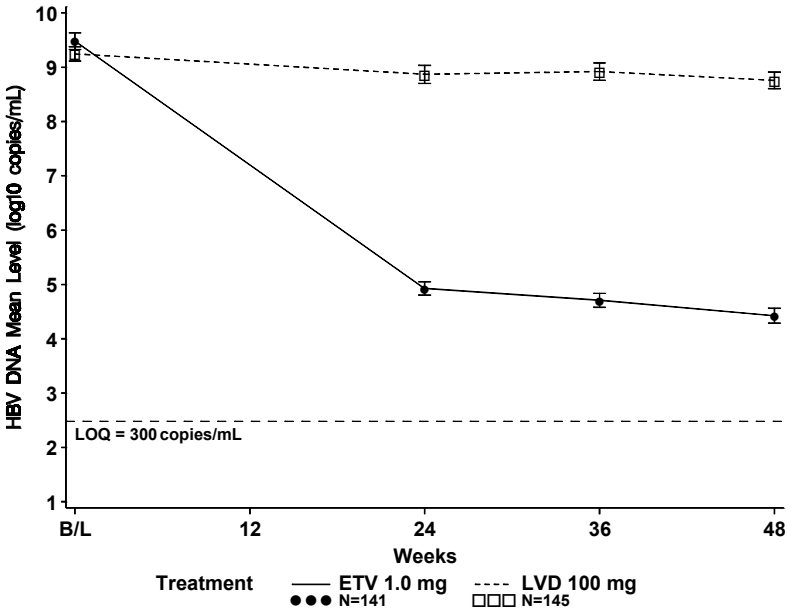
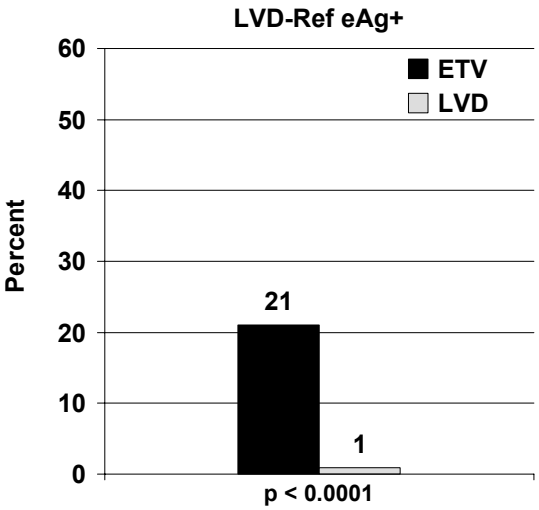


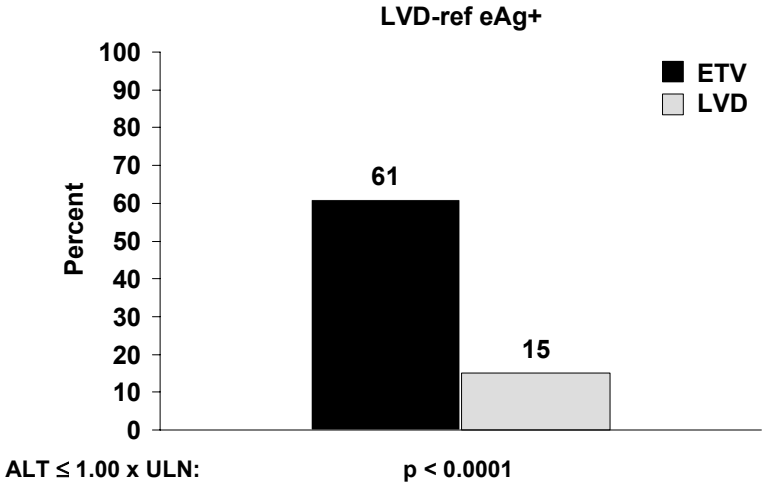
Figure 5.2.3.2C Proportion of Patients with HBV DNA < 400 Copies/mL by PCR at Week 48, LVD-Refractory Patients



ALT Normalization

ETV 1.0 mg was superior to continued LVD 100 mg for the proportion of patients who achieved ALT normalization (≤ 1 × ULN) at Week 48 (ETV 61% vs LVD 15%; p < 0.0001) (Table 5.2.3.2, Figure 5.2.3.2D).

Figure 5.2.3.2D Proportion of Patients with ALT Normalization at Week 48, LVD-Refractory Patients



Antigen Loss and Seroconversion

All patients in AI463026 were HBeAg-positive at the time of enrollment. ETV 1.0 mg was superior to continued LVD 100 mg for the proportion of patients who had loss of HBeAg at Week 48 (ETV 10% vs LVD 3%, difference estimate [ETV - LVD] = 6.5; 95% CI [0.7, 12.2], p = 0.0278). The proportions of ETV- and LVD-treated patients having HBe seroconversion at Week 48 were similar, and favored ETV (Table 5.2.3.2). The low absolute rate of HBe seroconversion in this LVD-refractory population may reflect that the study indirectly selected for an inherent, immunologic inability to make this response. Of note, 45% of ETV-treated patients and 54% of LVD-treated patients had prior IFN experience, while the mean duration of prior LVD therapy was 2.7 years for both treatment groups; therefore, the individuals enrolled in this study had had extensive prior opportunities to mount an HBeAb response and had been previously

unable to do so. It is reasonable to conclude that the spontaneous HBe seroconversion rates reported in the literature for an average population of patients with chronic HBV infection (approximately 10%) may not provide an appropriate comparison for this study population. All patients in this study had detectable serum HBsAg at baseline, and none lost HBsAg at Week 48.

Sustained Response Off Therapy

An assessment of sustained response to therapy among LVD-refractory patients was limited by the number of patients who demonstrated a combined virologic and serologic response (HBV DNA < 0.7 MEq/mL by bDNA assay *and* loss of HBeAg) at Week 48 (ETV 13 patients and LVD 1 patient). Of the 13 ETV-treated patients, five patients maintained a sustained response for the combined virologic and serologic endpoint at off-treatment Week 24; the single LVD-treated patient had a sustained response for this endpoint (Table 5.2.3.2).

5.3 Exploratory Analyses

5.3.1 Subpopulation Analyses

Efficacy results for ETV were analyzed to assess for consistency of effect across subgroups. Subgroups were defined based on standard subpopulation categories for the following variables: age (16 to 20, 21 to 64, and ≥ 65 years); race (White, Asian, and Other); gender; and HBV subtype (A, B, C, D, and Other). Of note, race and HBV subtype are both confounded with region, and the first two factors are the ones most likely to have a plausible biologic effect on the pathophysiology of this infectious disease. The endpoints assessed were those that have relevance to the clinical assessment of individual patient response (Histologic Improvement, ALT normalization, and HBV DNA as proportions below a relevant cutoff), rather than those that assess a population response. Associations between the baseline subgroups and the Week 48 endpoints were examined. Conclusions were based on Fisher's exact test with p-value < 0.01 considered to be significant. Results for these analyses are presented in Table 5.3.1A, 5.3.1B, and 5.3.1C for nucleoside-naive HBeAg-positive, nucleoside-naive HBeAg-negative, and LVD-refractory patients, respectively.

ETV response rates were consistent in magnitude across all subpopulations. No specific subset within the described categories was identified as having an inadequate response to ETV.

Table 5.3.1A: Subgroup Analyses, Nucleoside-Naive, HBeAg-Positive Patients (AI463022)

Baseline Category	Number with Response/Number Assessed (%)		
	Histologic Improvement	ALT ≤ 1 × ULN	HBV DNA < 400 copies/mL by PCR
Race: N (%)			
White	89/121 (74)	102/140 (73)	93/140 (66)
Asian	130/183 (71)	134/204 (66)	146/204 (72)
Other	7/ 10 (70)	6/ 10 (60)	7/10 (70)
Gender: N (%)			
Male	175/245 (71)	182/274 (66)	184/274 (67)
Female	51/ 69 (74)	60/ 80 (75)	62/80 (78)
Age (Years)			
16-20	23/26 (88)	23/28 (82)	13/28 (46)
21-64	191/275 (69)	211/312 (68)	224/312 (72)
≥ 65	12/13 (92)	8/14 (57)	9/14 (64)
Baseline HBV Subtype: N (%)			
A	60/ 85 (71)	64/ 94 (68)	62/94 (66)
B	46/ 61 (75)	47/ 68 (69)	45/68 (66)
C	72/102 (71)	80/111 (72)	87/111 (78)
D	22/ 31 (71)	26/ 37 (70	23/37 (62)
Other	26/ 35 (74)	25/ 44 (57)	29/44 (66)

Table 5.3.1B Subgroup Analyses, Nucleoside-Naive, HBeAg-Negative Patients (AI463027)

Baseline Category	Number with Response/Number Assessed (%)		
	Histologic Improvement	ALT ≤ 1 × ULN	HBV DNA <400 copies/mL by PCR
Race: N (%)			
White	121/171 (71)	147/193 (76)	174/193 (90)
Asian	80/117 (68)	96/122 (79)	114/122 (93)
Other	7/ 8 (88)	10/ 10 (100)	9/10 (90)
Gender: N (%)			
Male	162/225 (72)	190/248 (77)	227/248 (92)
Female	46/ 71 (65)	63/ 77 (82)	70/77 (91)

Table 5.3.1B Subgroup Analyses, Nucleoside-Naive, HBeAg-Negative Patients (AI463027)

Baseline Category	Number with Response/Number Assessed (%)		
	Histologic Improvement	ALT ≤ 1 × ULN	HBV DNA <400 copies/mL by PCR
Age (Years)			
16-20	3/ 3 (100)	3/3 (100)	2/3 (67)
21-64	199/284 (70)	242/312 (78)	286/312 (92)
≥ 65	6/ 9 (67)	8/10 (80)	9/10 (90)
Baseline HBV Subtype: N (%)			
A	17/ 25 (68)	26/ 33 (79)	30/33 (91)
B	24/ 44 (55)	34/ 46 (74)	41/46 (89)
C	42/ 54 (78)	46/ 57 (81)	55/57 (96)
D	100/ 144 (69)	122/157 (78)	142/157 (90)
Other	25/ 29 (86)	25/ 32 (78)	29/32 (91)

Table 5.3.1C Subgroup Analyses, LVD-Refractory Patients (AI463026)

Baseline Category	Number with Response/Number Assessed (%)		
	Histologic Improvement	ALT ≤ 1 × ULN	HBV DNA <400 copies/mL by PCR
Race: N (%)			
White	39/71 (55)	48/ 83 (58)	16/83 (19)
Asian	29/52 (56)	38/ 57 (67)	13/57 (23)
Other	0/1 (0)	0/ 1 (0)	0/1 (0)
Gender: N (%)			
Male	51/94 (54)	62/105 (59)	24/105 (23)
Female	17/30 (57)	24/ 36 (67)	5/36 (14)
Age (Years)			
16-20	9/ 13 (69)	10/ 15 (67)	1/15 (7)
21-64	57/105 (54)	73/120 (61)	27/120 (23)
≥ 65	2/ 6 (33)	3/ 6 (50)	1/6 (17)
Baseline HBV Subtype: N (%)			
A	18/ 33 (55)	19/ 37 (51)	12/37 (32)
B	14/ 21 (67)	14/ 23 (61)	7/23 (30)
C	14/ 26 (54)	22/ 27 (81)	5/27 (19)
D	17/35 (49)	28/ 45 (62)	4/45 (9)
Other	5/9 (56)	3/ 9 (33)	1/9 (11)

5.3.2 Predictors of Response

Two approaches were used to identify predictors of Week 48 response. Both baseline HBV disease characteristics and Week 24 response parameters were investigated as potential predictors of the following Week 48 endpoints: Histologic Improvement, HBV DNA < 400 copies/mL, ALT ≤ 1 × ULN, and seroconversion (for studies in HBeAg-positive patients). This analysis was applied to data for ETV-treated patients from the Phase 3 studies. Baseline parameters of interest included Knodell necroinflammatory and fibrosis scores, HBV DNA and ALT; parameters at Week 24 include HBV DNA and ALT. Conclusions were based on the Fisher's Exact test and the Cochran-Armitage trend test, with p-values < 0.01 considered to be significant. Results of these analyses are summarized below.

Baseline Predictors of Week 48 Endpoints:

- The baseline Knodell necroinflammatory score was the most consistent predictor for Week 48 endpoints (Table 5.3.2A). Higher necroinflammatory scores were associated with higher response rates for Histologic Improvement among all three study populations. Among nucleoside-naive, HBeAg-positive patients higher necroinflammatory scores were associated with higher response rates for HBV DNA < 400 copies/mL, ALT normalization, and seroconversion.
- Among nucleoside-naive HBeAg-positive patients, higher baseline Knodell fibrosis scores and higher ALT levels were associated with higher response rates for HBV DNA < 400 copies/mL.
- Lower baseline HBV DNA levels ($<10^9$ copies/mL for nucleoside-naive patients and $<10^7$ for LVD-refractory patients) were associated with higher response rates for HBV DNA < 400 copies/mL.

Week 24 Predictors of Week 48 Endpoints

HBV DNA level at Week 24 was the most consistent predictor for Week 48 endpoints (Table 5.3.2B).

- An HBV DNA $<10^3$ copies/mL at Week 24 was associated with higher Week 48 response rates for the following endpoints within the populations indicated: Histologic Improvement (nucleoside-naive HBeAg-positive); HBV DNA < 400 copies/mL (all three populations); ALT normalization (nucleoside-naive HBeAg-positive) and seroconversion (both HBeAg-positive populations).
- Lower ALT levels at Week 24 were associated with higher response rates for ALT normalization for all three populations studied.

Table 5.3.2A: Week 48 Endpoints by Baseline Measurements - ETV-Treated Patients

Baseline Measurement	Week 48 Endpoint Number in Response/Number Evaluable (%)		
	Nucleoside-Naive		LVD-Refractory
	HBeAg-Positive	HBeAg-Negative	HBeAg-Positive
	Histologic Improvement[b]		
Knodell Necroinflammatory Score			
2 - 4	9/ 33 (27)	9/ 33 (27)	5/ 26 (19)
5 - 7	67/105 (64)	56/ 90 (62)	29/ 47 (62)
8 - 10	98/118 (83)	103/127 (81)	23/ 39 (59)
11 - 14 (max)	52/ 58 (90)	40/ 46 (87)	11/ 12 (92)
	HBV DNA < 400 Copies/mL by PCR[a]		
Knodell Necroinflammatory Score			
2 - 4	13/ 33 (39)	32/ 33 (97)	3/ 26 (12)
5 - 7	65/105 (62)	82/ 90 (91)	9/ 47 (19)
8 - 10	94/118 (80)	117/127 (92)	10/ 39 (26)
11 - 14 (max)	54/ 58 (93)	43/ 46 (93)	5/ 12 (42)
Knodell Fibrosis Score			
0	1/ 2 (50)	4/ 4 (100)	0/ 1
1	127/200 (64)	149/162 (92)	16/ 76 (21)
3	74/87 (85)	103/111 (93)	8/ 33 (24)
4	24/ 25 (96)	18/ 19 (95)	3/ 14 (21)
HBV DNA by PCR			
$< 10^7$ copies/mL	24/ 25 (96)	104/113 (92)	8/ 11 (73)
10^7 - $< 10^8$ copies/mL	31/ 34 (91)	65/ 70 (93)	2/ 11 (18)
10^8- $< 10^9$ copies/mL	65/ 78 (83)	67/ 68 (99)	5/ 33 (15)
10^9 - $< 10^{10}$ copies/mL	68/ 98 (69)	51/ 59 (86)	6/ 52 (12)
$\geq 10^{10}$ copies/mL	57/117 (49)	10/ 14 (71)	8/ 34 (24)
ALT			
< 2 × ULN	82/139 (59)	103/115 (90)	10/66 (15)
2 × ULN - 5 × ULN	113/158 (72)	143/154 (93)	13/ 55 (24)
> 5 × ULN	51/ 57 (89)	51/56 (91)	6/ 20 (30)

Table 5.3.2A: Week 48 Endpoints by Baseline Measurements - ETV-Treated Patients

	Week 48 Endpoint Number in Response/Number Evaluable (%)		
	Nucleoside-Naive		LVD-Refractory
Baseline Measurement	**HBeAg-Positive**	**HBeAg-Negative**	**HBeAg-Positive**
		ALT ≤ 1 × ULN[b]	
Knodell Necroinflammatory Score			
2 - 4	12/ 33 (36)	27/ 33 (82)	16/26 (62)
5 - 7	71/105 (68)	65/ 90 (72)	31/ 47 (66)
8 - 10	87/118 (74)	105/127 (83)	23/ 39 (59)
11 - 14 (max)	51/ 58 (88)	38/ 46 (83)	8/ 12 (67)
		Seroconversion[c]	
Knodell Necroinflammatory Score			
2 - 4	0/ 33	n/a	1/ 26 (4)
5 - 7	18/105 (17)	n/a	2/ 47 (4)
8 - 10	33/118 (28)	n/a	4/ 39 (10)
11 - 14 (max)	20/ 58 (34)	n/a	4/ 12 (33)
ALT			
< 2 × ULN	16/139 (12)	n/a	3/ 66 (5)
2 × ULN - 5 × ULN	36/158 (23)	n/a	5/ 55 (9)
> 5 × ULN	22/ 57 (39)	n/a	3/ 20 (15)

[a] The analysis method is NC = F.

[b] Evaluable Baseline.

Table 5.3.2B Week 48 Endpoints by Week 24 Measurements - ETV-Treated Patients

	Week 48 Endpoint Number in Response/Number Evaluable (%) [d]		
	Nucleoside-Naive		LVD-Refractory
Week 24 Measurement	**HBeAg-Positive**	**HBeAg-Negative**	**HBeAg-Positive**
		Histologic Improvement	
HBV DNA by PCR			
< 400 copies/mL	118/144 (82)	162/206 (79)	7/ 11 (64)
400 - < 1000 copies/mL	31/ 33 (94)	12/ 18 (67)	5/ 6 (83)
1000 - < 100000 copies/mL	60/ 91 (66)	29/ 35 (83)	22/ 36 (61)
≥ 100000 copies/mL	8/ 11 (73)	3/ 3 (100)	33/ 56 (59)

Table 5.3.2B Week 48 Endpoints by Week 24 Measurements - ETV-Treated Patients

	Week 48 Endpoint Number in Response/Number Evaluable (%) [d]		
	Nucleoside-Naive		LVD-Refractory
Week 24 Measurement	HBeAg-Positive	HBeAg-Negative	HBeAg-Positive
	HBV DNA < 400 Copies/mL by PCR		
HBV DNA by PCR			
< 400 copies/mL	153/159 (96)	240/247 (97)	11/ 12 (92)
400 - < 1000 copies/mL	28/ 34 (82)	20/ 21 (95)	5/ 6 (83)
1000 - < 100000 copies/mL	47/118 (40)	32/ 38 (84)	10/ 46 (22)
≥ 100000 copies/mL	6/ 15 (40)	1/ 4 (25)	2/ 68 (3)
	ALT ≤ 1 × ULN		
HBV DNA by PCR			
< 400 copies/mL	129/160 (81)	119/249 (80)	10/ 12 (83))
400 - < 1000 copies/mL	22/ 34 (65)	16/ 21 (76)	5/ 6 (83)
1000 - < 100000 copies/mL	69/119 (58)	33/ 39 (85)	29/ 47 (62)
≥ 100000 copies/mL	10/ 16 (63)	2/ 4 (50)	41/ 68 (60)
ALT			
≤ 1 × ULN	172/190 (91)	211/232 (91)	49/57 (86)
> 1 × ULN - < 2 × ULN	52/108 (48)	41/83 (49)	29/51 (57)
2 × ULN - 5 × ULN	16/ 41 (39)	1/ 2 (50)	7/ 24 (29)
> 5 × ULN	2/ 6 (33)	0/0	1/ 2 (50)
	Seroconversion		
HBV DNA by PCR			
< 400 copies/mL	47/159 (30)	n/a	5/ 12 (42)
400 - < 1000 copies/mL	8/ 34 (24)	n/a	1/ 6 (17)
1000 - < 100000 copies/mL	14/117 (12)	n/a	4/ 46 (9)
≥ 100000 copies/mL	2/ 15 (13)	n/a	1/ 68 (1)

[c] Includes patients with measurements for both endpoints.

5.4 Efficacy in Special Populations

Two studies in special populations are ongoing: AI463038 (HBV/HIV coinfection) and AI463048 (decompensated liver disease). Preliminary efficacy results for these studies are presented below.

5.4.1 Patients with HBV/HIV Co-infection

Study AI463038 is a randomized, double-blind study of ETV compared with PBO in HBV/HIV co-infected patients who were LVD-refractory (recurrence of HBV viremia while receiving LVD for the treatment of HIV). Patients continued their LVD-containing highly active antiretroviral treatment (HAART) (LVD 300 mg/day) and were randomized 2:1 to add blinded ETV 1.0 mg or PBO for 24 weeks, at which point open-label ETV was offered to all patients for an additional 24 weeks. The blinded phase is complete and the open-label phase is ongoing.

At baseline, these patients had a mean serum HBV DNA by PCR of 9.13 $\log_{10}$ copies/mL and a mean ALT level of 71.5 U/L. Most patients were HBeAg-positive at baseline. The randomization yielded 51 patients who received ETV and 17 who received PBO. The primary efficacy endpoint was the mean reduction in HBV DNA by PCR at Week 24. ETV 1.0 mg was superior to PBO, with a mean decrease in HBV DNA of -3.65 $\log_{10}$ copies/mL vs +0.11 $\log_{10}$ copies/mL, respectively (difference estimate [ETV-PBO] = -3.75; 95% CI [-4.47, -3.04]; $p < 0.0001$). A treatment difference was observed as early as Week 2 and continued to increase through Week 24. The proportions of patients who had a baseline ALT value > 1.0 × ULN and who achieved ALT normalization (≤1 × ULN) at Week 24 were 34% (12/35) for ETV and 8% (1/12) for PBO (difference estimate [ETV-PBO] = 26.0; 95% CI (3.8, 48.1]; $p = 0.08$).

5.4.2 Patients with Decompensated Liver Disease

Study AI463048 is an open-label, randomized, 96-week study of ETV 1.0 mg compared with ADV 10 mg in patients with chronic HBV infection who have evidence of hepatic decompensation (Child-Pugh score of ≥ 7). The primary efficacy endpoint is the mean change in HBV DNA by PCR at Week 24. The target sample size is 270 randomized patients and enrollment is ongoing.

Data from 52 patients who received at least 12 weeks of study therapy were available for a preliminary assessment of efficacy: 30 received ETV 1.0 mg and 22 received ADV 10 mg. Due to the small sample size, only descriptive statistics are provided for this summary.

At baseline, the mean serum HBV DNA by PCR in the ETV group was comparable to that in the ADV group (ETV 7.34 $\log_{10}$ copies/mL; ADV 7.38 $\log_{10}$ copies/mL). The mean reductions in HBV DNA by PCR at Week 24 were 4.45 $\log_{10}$ copies/mL for ETV and 2.80 $\log_{10}$ copies/mL for ADV. A difference between treatment groups of approximately 1 $\log_{10}$ copies/mL in mean HBV DNA was observed as early as Week 4 and was maintained through Week 24.

5.5 Summary of Efficacy Evaluation

In nucleoside-naive, HBeAg-positive and HBeAg-negative patients, ETV 0.5 mg was superior to LVD 100 mg for the primary endpoint, Histologic Improvement. Treatment with ETV also demonstrated superiority in all assessments of virologic suppression. ETV 0.5 mg was superior to LVD 100 mg for normalization of ALT in both HBeAg-positive and HBeAg-negative patients.

In LVD-refractory patients, ETV 1.0 mg was superior to continued LVD 100 mg for the co-primary endpoints, Histologic Improvement and the Composite Endpoint (HBV DNA < 0.7 MEq/mL by bDNA assay *and* ALT < 1.25 × ULN). Treatment with ETV also demonstrated superiority for a variety of secondary efficacy endpoints that included improvement in necroinflammation and fibrosis, all assessments of virologic suppression, normalization of ALT, and loss of HBeAg.

6 RESISTANCE

6.1 In Vitro Resistance

In transient HBV culture systems, ETV displayed potent antiviral activity against both WT and LVD^R HBV. ETV inhibited the replication of LVD^R HBV, but at 8-fold higher concentrations than for the WT virus. Despite the decreased susceptibility of LVD^R HBV to ETV, the potency of ETV was still greater than that of either LVD or ADV for LVD^R strains of HBV.[5] Also, at extracellular concentrations representative of plasma levels in ETV-treated patients, intracellular ETV-TP accumulated to levels that are expected to inhibit the enzymatic activity of the LVD^R HBV polymerase. Finally, there was no *in vitro* evidence for cross-resistance between ADV and ETV[18,19] nor for any functional

interference between ETV and other nucleoside/nucleotide analogues used for the treatment of either HBV or HIV.

6.2 Clinical Resistance

Early clinical information about ETV resistance was obtained from two Phase 2 patients who developed rising viremia while on extended (> 1 year) ETV treatment. Both patients were nucleoside-experienced prior to their treatment with ETV, and isolates from both had LVD^R substitutions (rtL180M, rtM204V/I) present at baseline. Investigations using on-treatment isolates from these two patients demonstrated genotypic changes at residues rtT184, rtS202, and/or rtM250, which proved to be associated with decreased ETV susceptibility. However, further *in vitro* work demonstrated that introduction of these particular substitutions into recombinant viruses resulted in significant reductions in susceptibility to ETV only when LVD^R substitutions were also present.[18] This clinical information, together with the earlier *in vitro* work showing that LVD^R substitutions result in an 8-fold reduction in HBV susceptibility to ETV, provided guidance for the resistance investigations in the Phase 3 studies.

Current understanding regarding the frequency of ETV resistance in the clinical setting is based on analyses of baseline and on-treatment specimens from >700 patients treated with ETV in four studies. Data for nucleoside-naive patients were derived from AI463022 and AI463027, while data for LVD-refractory patients were derived from AI463026 and AI463014 (ETV 1.0-mg group). Sampling from the nucleoside-naive studies used baseline and Week 48 samples from >530 (>80%) of the nucleoside-naive ETV-treated patients and was supplemented by samples from all patients with viral rebound (defined as any increase in HBV DNA by ≥ 1 $\log_{10}$ by PCR from on-treatment nadir). Resistance testing in the LVD-refractory studies was performed on all available patient samples.

None of the nucleoside-naive patients had either genotypic or phenotypic evidence for ETV resistance emergence through the earlier of the last study visit or the Week 48 visit. Fourteen (2.1%) of ETV-treated nucleoside-naive patients (6 from AI463022 and 8 from AI463027) experienced a viral rebound on treatment, although none showed genotypic or phenotypic evidence for emerging ETV resistance. Among the 183 LVD-refractory, ETV-treated patients, 5 (2.7%) exhibited a virologic rebound during the first year of

treatment, with rebounds in only 2 of 4 cases examined attributable to the presence of substitutions associated with ETV^R.

ETV^R substitutions can be selected by LVD, as they preexisted in at least 29 patients (including 6 detected using a highly sensitive detection assay) harboring LVD^R virus, but in none of the nucleoside-naive patients. ETV does not select for LVD^R substitutions *de novo* or for other novel substitutions beyond those at residues rtT184, rtS202, and rtM250 that are associated with increased phenotypic resistance to ETV. There was a strong correlation between the population wildtype phenotype (EC_{50} of ≤ 3 nM) of viruses at baseline and the maximal ETV antiviral efficacy in treated patients. Patients experiencing virologic rebound due to the emergence of resistance harbored viruses at Week 48 with ETV population susceptibility phenotypes of 87 and 986 nM; thus, a population susceptibility phenotype of approximately 100 nM may represent a potential threshold for clinically relevant resistance.

6.3 Summary of Resistance Evaluation

In transient HBV culture systems, ETV was the most potent nucleoside antiviral against LVD^R HBV, despite its reduced susceptibility to ETV relative to WT HBV. These cell-based assays demonstrated that the presence of LVD^R substitutions rtL180M and rtM204V in HBV clones resulted in an 8-fold decrease in viral susceptibility to ETV. Addition of ETV^R substitutions at rtT184, rtS202, rtM250V or the combination of rtT184G and rtS202I substitutions reduced ETV susceptibility 16 to 70, 11 to 100, 113-242, and > 741-fold, respectively.

Treatment with ETV did not result in the emergence of viral resistance, either to ETV or LVD, in nucleoside-naive patients following 48 weeks of treatment. ETV was effective in patients harboring LVD^R HBV, despite the reduced susceptibility of LVD^R virus. Although genotypic changes associated with resistance to ETV can be present among patients who are LVD-refractory, the rate at which this occurs is limited and virologic rebounds due to resistance were infrequently observed (1%) during the first year of treatment.

7 CLINICAL SAFETY

7.1 Safety Methodology

Integrated safety analyses across the ETV development program were performed at two levels. The design of the Phase 3 studies permitted a direct comparison of the general safety of ETV with the safety of LVD in treatment populations (nucleoside-naive and LVD-refractory) which had comparable size and disease characteristics. Analyses for infrequent events (eg, malignant neoplasms) were performed on a larger, more diverse population, referred to as the Safety Cohort, using data integrated across 10 Phase 2 and 3 studies.

The integrated general safety analyses were performed within the two populations described below:

- nucleoside-naive: 1347 treated patients (ETV 679, LVD 668) from AI463022 and AI463027
- LVD-refractory: 373 treated patients (ETV 183, LVD 190) from AI463026 (all patients) and AI463014 (patients in the ETV 1.0 mg and LVD treatment groups only)

The nucleoside-naive and LVD-refractory populations were analyzed separately for the following reasons. First, total duration of nucleoside analogue exposure was greater for the LVD-refractory population than for the nucleoside-naive population, since the LVD-refractory population had extensive prior HBV therapy. Second, the ETV drug exposure for LVD-refractory patients was higher than for nucleoside-naive patients, due to the higher dose of ETV used in the former: 1.0 mg QD versus 0.5 mg QD, respectively. Third, the LVD-refractory population may have a more complex safety profile than the nucleoside-naive population. In particular, LVD-refractory patients on continued LVD are unlikely to experience substantial improvement in virologic suppression while on blinded treatment and are therefore more likely to have active disease progression while under study observation.

The larger Safety Cohort population includes a greater diversity of patients that are not evenly distributed between ETV and LVD; however the larger size increases the sensitivity in detecting differences between treatment groups in rates of infrequent events. Rates for death and malignant neoplasms were assessed within the Safety Cohort, and

this population was also screened for events that might be related to abnormalities in lactate. Safety Cohort analyses were performed using data for all treated patients from 10 Phase 2/3 studies (Table 7.1).

Table 7.1: Safety Cohort

Protocol	Study Type	Treatment (PO, QD)	Number of Patients Treated
AI463022	Nucleoside-naive, HBeAg+	ETV 0.5 mg LVD 100 mg	354 355
AI463027	Nucleoside-naive, HBeAg– /HBeAb+	ETV 0.5 mg LVD 100 mg	325 313
AI463026	LVD-refractory HBeAg+	ETV 1.0 mg LVD 100 mg	141 145
AI463014	LVD-refractory HBeAg+ or -	ETV 0.1, 0.5, 1.0 mg LVD 100 mg	136 45
AI463004	Nucleoside-naive or LVD-refractory	ETV 0.05, 0.1, 0.5, 1.0 mg PBO	34 8
AI463007	Long-Term, open-label (rollover for AI463004)	ETV 0.1 mg	(28)
AI463005	Nucleoside-naive, immunocompetent	ETV 0.01, 0.1, 0.5 mg LVD 100 mg	136 41
AI463012	Nucleoside-naive, immunocompetent (China)	ETV 0.1, 0.5 mg PBO	141 71
AI463015	OLT recipients	ETV 1.0 mg	9
AI463056	LVD-failure (China)	ETV 1.0 mg PBO	116 29
TOTAL		**ETV** **LVD** **PBO**	**1392** **899** **108**[a]
TOTAL- ALL POPULATIONS			**2399**

[a] Of the 108 patients who received PBO, 105 later received open-label ETV in rollover studies.

In addition to the integrated analyses, safety information is presented separately for two ongoing studies in special populations:

- AI463038 in HBV/HIV co-infected patients (N = 68: ETV 51, PBO 17)
- AI463048 in patients with hepatic decompensation (Child-Pugh score of ≥ 7) (N = 62: ETV 32, ADV 30)

All safety analyses include data for all treated patients within the specified analysis population. All on-treatment safety tabulations are cumulative, from the first dose of study drug to the last observation on-treatment regardless of when that occurred in relation to efficacy assessments (eg, data are not censored for safety at 1 year of treatment).

7.2 Extent of Exposure

7.2.1 Nucleoside-naive Patients

The integrated analyses for nucleoside-naive patients included 1347 treated patients (ETV 679; LVD 668). The mean time on assigned therapy was 65.9 weeks for the ETV group and 60.8 weeks for the LVD group. The mean duration of off-treatment follow-up was 22 weeks for the ETV group and 19 weeks for the LVD group.

7.2.2 LVD-refractory Patients

The integrated analyses for LVD-refractory patients included 373 treated patients (ETV 183; LVD 190). The mean time on assigned therapy was 68.2 weeks for the ETV group and 51.1 weeks for the LVD group. The mean duration of off-treatment follow-up was 15 weeks for the ETV group and 13 weeks for the LVD group.

7.2.3 Safety Cohort

Across the 10 integrated studies, a total of 1392 patients received initial study treatment with blinded ETV; 899 received initial treatment with blinded LVD; and 108 received an initial regimen of PBO. Of the 108 PBO patients, 105 subsequently received open-label ETV and are included in the any-ETV treatment group for all Safety Cohort analyses. Therefore, the total number of patients who received either blinded or open-label ETV was 1497. Of the 1497 patients, 751 (50%) received treatment for ≥ 1 year, 337 (23%) for ≥1.5 years, and 40 (3%) for ≥ 2 years. A larger proportion of patients treated with ETV (23%) received study drug for ≥ 1.5 years than did patients treated with LVD (17%). One patient randomized to LVD inadvertently received ETV in addition to LVD. In the Safety Cohort analyses, this patient was assessed as randomized (LVD group).

7.3 General Safety

7.3.1 Deaths, Serious Adverse Events, and Adverse Events Associated with Discontinuation of Study Therapy

Deaths

In both nucleoside-naive and LVD-refractory populations, the number of deaths was low and comparable between treatments: 3 ETV and 6 LVD (Table 7.3.1). None of these deaths was assessed by the investigator as related to study drug, and the causes were consistent with chronic HBV infection or with other co-morbid disease. Deaths reported in the Safety Cohort are discussed in Section 7.5.1.

Serious Adverse Events

Within each analysis population, the frequency of on-treatment serious adverse events (SAEs) was comparable between treatments (Table 7.3.1). In the nucleoside-naive population, only three SAE terms were reported in more than two patients in either treatment group: increased ALT (ETV 1 [< 1%]; LVD 6 [< 1%]), pyrexia (ETV 0; LVD 3 [< 1%]), and hepatic neoplasm malignant (ETV 3 [< 1%]; LVD 2 [< 1%]). In the LVD-refractory population, no SAE was reported in more than one patient in either treatment group. SAEs occurred with comparable frequency in the nucleoside-naive and LVD-refractory populations (Table 7.3.1).

Adverse Events Associated with Discontinuation of Study Therapy

Within each analysis population, fewer ETV-treated patients discontinued study drug due to an adverse event than did LVD-treated patients. This treatment difference was largely driven by the number of discontinuations due to ALT elevations (nucleoside-naive ETV 1 vs LVD 6; LVD-refractory ETV 0 vs LVD 7), which was the single most frequent reason for discontinuation. Discontinuations due to adverse events occurred with comparable frequency in the nucleoside-naive and LVD-refractory populations (Table 7.3.1).

Table 7.3.1 Summary of Safety Results

	Number (%) of Patients			
	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
Deaths[a]	2 (0.3)	4 (0.6)	1 (0.5)	2 (1.1)
SAEs	48 (7)	54 (8)	19 (10)	14 (7)
Discontinuation due to AE	7 (1)	18 (3)	4 (2)	14 (7)
Due to ALT elevation	1 (<1)	6 (<1)	0	7 (4)

[a] All deaths on study.

7.3.2 Adverse Events

Overall, the types and frequency of adverse events were comparable between the ETV and LVD treatment groups. Moreover, the adverse event profiles were consistent between the nucleoside-naive and LVD-refractory populations. Adverse events were common on treatment, reflecting the underlying HBV infection of the study participants and the long duration of the observation period (up to 107 weeks).

Most adverse events were mild to moderate in severity (Grade 1 to 2). In both nucleoside-naive and LVD-refractory populations, the most common on-treatment adverse events (≥ 10% for either treatment group) were headache, upper respiratory tract infection, nasopharyngitis, cough, fatigue, and upper abdominal pain; these events occurred with comparable frequency between the ETV and LVD groups (Table 7.3.2A).

Table 7.3.2A: Most Common Clinical Adverse Events (Reported for at Least 10% of Patients in Any Treatment Group)

System Organ Class/ Adverse Event	Number (%) of Patients			
	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
Gastrointestinal				
Abdominal pain upper	68 (10)	63 (9)	15 (8)	24 (13)
General				
Fatigue	66 (10)	63 (9)	26 (14)	22 (12)
Infections and Infestations				
Upper respiratory tract infection	121 (18)	108 (16)	30 (16)	22 (12)
Nasopharyngitis	80 (12)	79 (12)	16 (9)	19 (10)
Nervous System				
Headache	137 (20)	128 (19)	35 (19)	34 (18)
Respiratory, Thoracic and Mediastinal				
Cough	73 (11)	65 (10)	20 (11)	17 (9)

Note: Laboratory abnormalities reported as adverse events by the investigator are excluded from the table

Grade 2 to 4 clinical adverse events (moderate to severe intensity) that occurred in ≥ 2% of patients in any treatment group are presented in Table 7.3.2B.

Table 7.3.2B: Clinical Adverse Events of Moderate to Severe Intensity (Grade 2 to 4) Reported for at Least 2% of Patients in Any Treatment Group

System Organ Class/ Adverse Event	Number (%) of Patients			
	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
Gastrointestinal				
Diarrhea	16 (2)	15 (2)	7 (4)	2 (1)
Abdominal pain	14 (2)	14 (2)	5 (3)	1 (<1)
Abdominal pain upper	12 (2)	13 (2)	4 (2)	9 (5)
Dyspepsia	6 (<1)	7 (1)	3 (2)	0
Nausea	10 (1)	4 (<1)	3 (2)	6 (3)

Table 7.3.2B: Clinical Adverse Events of Moderate to Severe Intensity (Grade 2 to 4) Reported for at Least 2% of Patients in Any Treatment Group

	Number (%) of Patients			
	Nucleoside-Naive		LVD-Refractory	
System Organ Class/ Adverse Event	**ETV 0.5 mg N=679**	**LVD 100 mg N=668**	**ETV 1.0 mg N=183**	**LVD 100 mg N=190**
General				
Fatigue	14 (2)	11 (2)	9 (5)	7 (4)
Pyrexia	13 (2)	11 (2)	8 (4)	4 (2)
Malaise	2 (<1)	2 (<1)	0	3 (2)
Infections/Infestations				
Upper respiratory tract	22 (3)	19 (3)	13 (7)	4 (2)
Influenza	20 (3)	11 (2)	2 (1)	3 (2)
Nasopharyngitis	12 (2)	14 (2)	7 (4)	3 (2)
Bronchitis	3 (<1)	3 (<1)	4 (2)	3 (2)
Pharyngitis	8 (1)	3 (<1)	3 (2)	2 (1)
Urinary tract infection	7 (1)	11 (2)	3 (2)	3 (2)
Hepatobiliary				
Hepatic function abnormal	0	0	0	3 (2)
Injury				
Skin laceration	2 (<1)	2 (<1)	3 (2)	0
Metabolic/Nutritional				
Hyperglycemia	2 (<1)	3 (<1)	4 (2)	0
Musculoskeletal				
Back pain	17 (3)	18 (3)	5 (3)	4 (2)
Arthralgia	15 (2)	9 (1)	2 (1)	5 (3)
Pain in extremity	3 (<1)	5 (<1)	4 (2)	2 (1)
Nervous System				
Headache	39 (6)	28 (4)	12 (7)	8 (4)
Respiratory				
Cough	15 (2)	12 (2)	5 (3)	5 (3)
Pharyngolaryngeal pain	10 (1)	7 (1)	4 (2)	0

Note: Laboratory abnormalities reported as adverse events by the investigator are excluded from the table

7.3.3 Laboratory Abnormalities

In general, laboratory abnormalities observed on treatment were comparable in type and frequency between the ETV and LVD groups. The frequency of selected treatment-emergent laboratory abnormalities is presented by treatment group and study population in Table 7.3.3A.

Table 7.3.3A: Selected Treatment-Emergent Laboratory Abnormalities

	Number with Abnormality/Number Assessed[a] (%)			
	Nucleoside-Naive		LVD-Refractory	
Laboratory Test[b]	**ETV 0.5 mg** N=679	**LVD 100 mg** N=668	**ETV 1.0 mg** N=183	**LVD 100 mg** N=190
Hemoglobin < 8.0 g/dL	1/665 (<1)	0/652	0/182	0/186
WBC < 1000/mm^3	0/634	0/621	0/167	0/174
Platelet < 50,000 /mm^3	0/647	0/637	0/174	0/181
Lipase ≥ 2.1 × ULN	24/373 (6)	23/375 (6)	10/119 (8)	6/121 (5)
Creatinine ≥ 0.5 mg/dL from baseline	7/675 (1)	9/657 (1)	3/183 (2)	2/189 (1)
Glucose[c]				
< 50 mg/dL	9/652 (1)	14/628 (2)	3/178 (2)	5/180 (3)
≥ 200 mg/dL	25/652 (4)	20/628 (3)	8/178 (4)	12/180 (7)

[a] For laboratory tests other than creatinine and glucose, number assessed represents patients who had a normal baseline value

[b] For hemoglobin, WBC, platelet, and lipase, the cutoffs capture all Grade 3 to 4 abnormalities

[c] Fasting or non-fasting; number assessed represents patients who had baseline values 50 to < 200 mg/dL

Hematology

The frequency of on-treatment hematologic abnormalities was low and comparable between ETV and LVD for both nucleoside-naive and LVD-refractory patients (Table 7.3.3B). Grade 3 to 4 abnormalities were reported infrequently. Although not unexpected in the chronic HBV population, increased prothrombin time (PT) and increased international normalized ratio (INR) were the most frequently reported

hematologic abnormalities in both populations. No treatment-emergent platelet abnormalities <50,000/mm^3 were observed in either population (Table 7.3.3A).

Table 7.3.3B: Hematologic Abnormalities (On-Treatment)

	Number with Abnormality/Number with Measurement (%)			
	Nucleoside-Naive		LVD-Refractory	
Laboratory Test	**ETV 0.5 mg N = 679**	**LVD 100 mg N = 668**	**ETV 1.0 mg N = 183**	**LVD 100 mg N = 190**
Hemoglobin				
Grade 1 - 4	20/ 675 (3)	18/ 658 (3)	8/ 183 (4)	11/ 189 (6)
Grade 3 - 4	1/ 675 (<1)	0/ 658	0/ 183	0/ 189
WBC				
Grade 1 - 4	130/675 (19)	138/ 658 (21)	39/ 183 (21)	40/ 189 (21)
Grade 3 - 4	0/ 675	0/ 658	0/ 183	0/ 189
Neutrophils				
Grade 1 - 4	61/ 675 (9)	62/ 658 (9)	16/ 183 (9)	24/ 189 (13)
Grade 3 - 4	2/ 675 (<1)	1/ 658 (<1)	4/ 183 (2)	1/ 189 (<1)
Platelets				
Grade 1 - 4	48/ 675 (7)	36/ 658 (5)	14/ 183 (8)	26/ 189 (14)
Grade 3 - 4	1/ 675 (<1)	1/ 658 (<1)	1/ 183 (<1)	1/ 189 (<1)
Prothrombin time				
Grade 1 - 4	208/569 (37)	181/551 (33)	58/ 169 (34)	64/ 179 (36)
Grade 3 - 4	9/ 569 (2)	3/ 551 (<1)	4/ 169 (2)	7/ 179 (4)
INR				
Grade 1 - 4	175/611 (29)	148/598 (25)	53/ 166 (32)	65/ 171 (38)
Grade 3 - 4	7/ 611 (1)	5/ 598 (<1)	3/ 166 (2)	7/ 171 (4)

Liver Function Tests

As expected in patients with chronic HBV infection, on-treatment elevations in ALT and aspartate aminotransferase (AST) were the most frequently reported laboratory abnormalities (Table 7.3.3C). Within each population, the frequency of on-treatment ALT abnormalities was comparable between ETV- and LVD-treated patients, as was the frequency of other liver function abnormalities (total bilirubin, alkaline phosphatase, and albumin). The frequency of liver function test abnormalities was also comparable between the nucleoside-naive and LVD-refractory populations. Assessments of ALT flare and liver function elevations from baseline are discussed in Section 7.4.

Table 7.3.3C: Liver Function Test Abnormalities (On-Treatment)

	Number with Abnormality/Number with Measurement (%)			
	Nucleoside-Naive		LVD-Refractory	
Laboratory Test	ETV 0.5 mg N = 679	LVD 100 mg N = 668	ETV 1.0 mg N = 183	LVD 100 mg N = 190
ALT				
Grade 1 - 4	593/676 (88)	586/658 (89)	165/183 (90)	181/189 (96)
Grade 3 - 4	140/676 (21)	170/658 (26)	35/183 (19)	59/ 189 (31)
AST				
Grade 1 - 4	472/675 (70)	477/655 (73)	128/183 (70)	156/189 (83)
Grade 3 - 4	48/675 (7)	64/655 (10)	12/183 (7)	37/189 (20)
Alkaline Phosphatase				
Grade 1 - 4	61/676 (9)	44/658 (7)	14/183 (8)	28/189 (15)
Grade 3 - 4	0/676	1/658 (<1)	0/183	0/189
Total Bilirubin				
Grade 1 - 4	219/675 (32)	169/658 (26)	60/183 (33)	60/189 (32)
Grade 3 - 4	13/675 (2)	13/658 (2)	5/183 (3)	3/189 (2)
Albumin				
Grade 1 - 4	44/674 (7)	45/655 (7)	15/ 181 (8)	28/ 187 (15)
Grade 3 - 4	2/ 674 (<1)	1/ 655 (<1)	0/ 181	1/ 187 (<1)

Renal Function Tests

Abnormal elevations in creatinine occurred with comparable frequency between ETV and LVD regardless of the population, but were observed more frequently in LVD-refractory patients than in nucleoside-naive patients (Table 7.3.3D). No on-treatment renal abnormalities were Grade 3 to 4 in severity. Only 1% to 2% of patients in any treatment group experienced a treatment-emergent elevation of ≥ 0.5 mg/dL in creatinine from baseline (Table 7.3.3A).

Table 7.3.3D: Renal Function Test Abnormalities (On-Treatment)

	Number with Abnormality/Number with Measurement (%)			
	Nucleoside-Naive		LVD-Refractory	
Laboratory Test	ETV 0.5 mg N = 679	LVD 100 mg N = 668	ETV 1.0 mg N = 183	LVD 100 mg N = 190
BUN/Urea				
Grade 1 - 4	23/ 673 (3)	25/ 655 (4)	10/183 (5)	10/189 (5)
Grade 3 - 4	0/ 673	0/ 655	0/ 183	0/ 189
Creatinine				
Grade 1 - 4	24/676 (4)	34/658 (5)	22/183 (12)	19/ 189 (10)
Grade 3 - 4	0/ 676	0/ 658	0/ 183	0/ 189

Pancreatic Enzymes

Amylase and lipase elevations occur commonly in several populations with chronic viral disease, including HBV, and are infrequently associated with a diagnosis of clinical pancreatitis. In both nucleoside-naive and LVD-refractory populations, Grade 3 to 4 amylase and lipase abnormalities were infrequent in both treatment groups (Table 7.3.3E) and infrequently (< 1%) resulted in study drug discontinuation. Safety analyses for the ETV development program were performed as cumulative tabulations counting patients who had a single abnormal safety parameter. Pancreatic enzyme abnormalities were explored by serial cross-sectional analyses. These analyses demonstrated that the proportion of patients with an abnormal elevation in amylase or lipase at any one timepoint was comparable to the proportion with an abnormality at baseline (approximately 5% to 10%), and also that these proportions were stable over time. This observation suggests that amylase and lipase abnormalities are not associated with study drug administration in either treatment group.

Table 7.3.3E: Pancreatic Enzyme Abnormalities (On-Treatment)

	Number with Abnormality/Number with Measurement (%)			
	Nucleoside-Naive		LVD-Refractory	
Laboratory Test	**ETV 0.5 mg N = 679**	**LVD 100 mg N = 668**	**ETV 1.0 mg N = 183**	**LVD 100 mg N = 190**
Amylase				
Grade 1 - 4	170/670 (25)	163/ 652 (25)	47/183 (26)	53/188 (28)
Grade 3 - 4	17/ 670 (3)	14/ 652 (2)	7/183 (4)	7/188 (4)
Lipase				
Grade 1 - 4	106/429 (25)	100/ 417 (24)	42/137 (31)	51/141 (36)
Grade 3 - 4	33/ 429 (8)	28/417 (7)	11/137 (8)	10/141 (7)

Glucose

Dysregulation of glucose homeostasis has been associated with chronic hepatitis; reports in the literature show that between 9% to 13% of patients with chronic HBV infection have co-incident diabetes mellitus.[23] In the ETV clinical program, there was no requirement that glucose levels be obtained in the fasting state.

For both the nucleoside-naive and the LVD-refractory populations, fasting glucose abnormalities were observed with comparable frequency between treatment groups and were generally Grade 1 to 2 in severity (Table 7.3.3F). Grade 3 to 4 abnormalities in fasting values occurred in ≤ 3% of patients in either population. Analyses of glucose values, without regard to fasting status, demonstrated that small numbers of patients treated with ETV had treatment-emergent values at either extreme (< 50 and ≥ 200 mg/dL) at some timepoint during treatment (Table 7.3.3A).

Table 7.3.3F: Fasting Glucose Abnormalities (On-Treatment)

Laboratory Test	Number with Abnormality/Number with Measurement (%)			
	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
Hypoglycemia				
Grade 1 - 4	30/ 513 (6)	41/ 487 (8)	16/150 (11)	14/ 152 (9)
Grade 3 - 4	1/ 513 (<1)	1/ 487 (<1)	0/150	0/ 152
Hyperglycemia				
Grade 1 - 4	94/513 (18)	86/ 487 (18)	33/150 (22)	26/152 (17)
Grade 3 - 4	9/ 513 (2)	8/ 487 (2)	4/150 (3)	5/152 (3)

7.4 ALT Flares and Other Hepatic Safety Issues

Hepatic flares or exacerbations of hepatitis represent an important safety issue in the management of chronic HBV infection, regardless of the specific treatment intervention used. Definitions of this phenomenon are generally based on changes in ALT, which provides a non-specific but sensitive method of detection; therefore, the pathophysiologic mechanisms underlying hepatic flares are diverse. These include unrelated coincident pathology (eg, superimposed acute hepatitis A), worsening of HBV infection associated with increasing HBV DNA levels, virologic rebound due to drug-resistant HBV mutants, and an immunologically mediated inflammatory response associated with clearance or rapid reduction of plasma and tissue HBV DNA.

The ETV Phase 2/3 clinical program captured events that suggested an acute worsening of hepatic inflammation or acute impairment of hepatic function by identifying both ALT flares and SAE reports for specific event terms that could represent worsening hepatic function. The ETV program defined an ALT flare as an ALT 10 × ULN *and* 2 × baseline based on US National Institutes of Health (NIH) consensus criteria.[7,22] The additional analysis of SAE reports was intended to capture exacerbations of hepatitis occurring in patients with occult cirrhosis, who may have impaired hepatic reserve and may not be able to mount a change in ALT that would meet laboratory criteria for an ALT flare. Relevant SAE reports that reflect a change in hepatic function were defined by a list of

adverse event terms potentially associated with worsening hepatitis or hepatic decompensation. However, in the analyses of ALT flares and relevant SAEs, there can be extensive overlap between the two categories, since events meeting the ALT flare criteria were required to be reported as SAEs during the later parts of these trials.

ALT flares reported during the on-treatment and off-treatment follow-up periods are defined as follows:

- **On-treatment ALT flare**: an ALT measurement > 2 × baseline *and* > 10 × ULN through the end of study therapy plus 5 days
- **Off-treatment follow-up ALT flare**: an ALT measurement > 2 × reference *and* > 10 × ULN from the end of study therapy plus 6 days to the earlier of two events: (1) the start of alternative HBV therapy or (2) the end of follow-up

7.4.1 Nucleoside-Naive Patients

In nucleoside-naive patients, ALT flares were observed less frequently in the ETV group than in the LVD group during both the on-treatment and off-treatment periods (Table 7.4.1).

On-Treatment

On-treatment ALT flares were observed in 15 (2%) ETV-treated and 28 (4%) LVD-treated patients. ALT flares were generally not associated with signs or symptoms of worsening hepatic function for either treatment regimen. The occurrence of an ALT flare led to discontinuation of study drug in 4 patients: 1 in the ETV group and 3 in the LVD group.

Of the 15 ETV-treated patients who had an on-treatment ALT flare, 10 had at least a 2-$\log_{10}$ reduction in HBV DNA by bDNA assay during the 3 months before or after the ALT flare. All of the ETV-associated flares were self-limited without clinically important changes in hepatic function, and 14 of these 15 patients continued ETV treatment through the resolution of the flare.

Of the 28 LVD-treated patients who had an on-treatment ALT flare, 11 had at least a 2-$\log_{10}$ reduction in HBV DNA by bDNA during the 3 months before or after the ALT flare. On-treatment ALT flares for 12 LVD patients were associated with a ≥ 1 log rise in HBV DNA by bDNA. One of the LVD-treated patients who had an ALT flare in

association with rising HBV DNA had a complicated course resulting in an off-treatment death from hepatic decompensation.

Relevant SAE events were reported during the on-treatment period for < 1% of ETV-treated patients and 1% of LVD-treated patients. Most relevant SAE events on treatment were associated with ALT flares.

Off-Treatment

Off-treatment ALT flares were observed in 25 (6%) ETV-treated patients who were observed off-treatment and in 38 (10%) LVD-treated patients who were observed off-treatment (median duration of off-treatment observation: ETV 23.4 weeks; LVD 22.4 weeks). In general, off-treatment flares were associated with rising HBV DNA for both treatment groups: 18 of 25 ETV patients and 29 of 38 LVD patients had off-treatment flares associated with a ≥ 1 log rise in HBV DNA by bDNA. Among nucleoside-naive patients, the majority of off-treatment ALT flares occurred in HBeAg-negative patients: 23 of 25 for ETV and 29 of 38 for LVD. These observations are consistent with the biology of HBeAg-negative disease, which is associated with impaired immunologic control of HBV viremia and high relapse rates when antiviral therapy is stopped.

During off-treatment follow-up, relevant SAE events were reported in 2% of ETV-treated patients versus 3% of LVD-treated patients. Most relevant SAE events reported during off-treatment follow-up were associated with ALT flares.

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Table 7.4.1: ALT Flares - Nucleoside-Naive Patients

	Number of Patients (%)			
	On Treatment		Off-Treatment Follow-up	
	ETV 0.5 mg N = 679	LVD 100 mg N = 668	ETV 0.5 mg N = 431	LVD 100 mg N = 392
ALT flares	15 (2)	28 (4)	25 (6)	38 (10)
ALT flares with relevant clinical events and/or laboratory abnormalities	1 (<1)	6 (<1)	0	1 (<1)
Relevant clinical events during ALT flares	0	2 (<1)	0	0
ASCITES	0	1 (<1)	0	0
HEPATIC FAILURE	0	1 (<1)	0	0
Relevant laboratory abnormalities during ALT flares	1 (<1)	5 (<1)	0	1 (<1)
Albumin < 3.0 g/dL	1 (<1)	1 (<1)	0	0
Intl normalized ratio > 1.5 or prothrombin time >= 1.26 x ULN	0	4 (<1)	0	1 (<1)
Total bilirubin > 2.5 mg/dL and > 1 mg/dL increase from baseline	1 (<1)	2 (<1)	0	0

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7.4.2 LVD-Refractory Patients

On-Treatment

In LVD-refractory patients, on-treatment ALT flares were observed less frequently in ETV-treated patients (4, 2%) than in LVD-treated patients (21, 11%) (Table 7.4.2). In the ETV group, two of the four ALT flares occurred in association with a 2-$\log_{10}$ reduction in HBV DNA by bDNA (3 months before or after the flare). Three of four patients continued ETV through the flare. In contrast, 18 of the 21 ALT flares in the LVD group occurred in conjunction with HBV DNA values that remained flat and detectable by bDNA assay.

There were only four relevant SAE events during the on-treatment period and all occurred in LVD-treated patients. All four relevant SAE reports were reports of an ALT flare, and none of these events had relevant non-ALT laboratory abnormalities or clinical events in association with the ALT flare.

Off-Treatment

Off-treatment ALT flares were observed in 3 of 56 (5%) ETV-treated patients and none of 31 LVD-treated patients (median duration of off-treatment follow-up: ETV 14.2 weeks and LVD 11.4 weeks). In the ETV treatment group, 2 of 3 patients had off-treatment flares associated with a ≥ 1 log rise in HBV DNA by bDNA. The absence of off-treatment ALT flares for LVD may reflect the limited off-treatment experience in this population and is also consistent with poor on-treatment efficacy in these patients (ie, late withdrawal of failing therapy does not result in HBV DNA changes that elicit a subsequent immune response). None of the off-treatment flares in ETV-treated patients were associated with hepatic decompensation.

No relevant SAE events were reported during the off-treatment follow-up period for either treatment group.

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Table 7.4.2: ALT Flares - LVD-Refractory Patients

	Number of Patients (%)			
	On Treatment		Off-Treatment Follow-up	
	ETV 1.0 mg N = 183	LVD 100 mg N = 190	ETV 1.0 mg N = 56	LVD 100 mg N = 31
ALT flares	4 (2)	21 (11)	3 (5)	0
ALT flares with relevant clinical events and/or laboratory abnormalities	1 (<1)	2 (1)	0	0
Relevant clinical events during ALT flares	1 (<1)	1 (<1)	0	0
ASCITES	0	1 (<1)	0	0
HEPATIC FAILURE	0	1 (<1)	0	0
OCULAR ICTERUS	1 (<1)	0	0	0
PERITONITIS BACTERIAL	0	1 (<1)	0	0
Relevant laboratory abnormalities during ALT flares	1 (<1)	2 (1)	0	0
Albumin < 3.0 g/dL	0	1 (<1)	0	0
Intl normalized ratio > 1.5 or prothrombin time >= 1.26 x ULN	0	2 (1)	0	0
Total bilirubin > 2.5 mg/dL and > 1 mg/dL increase from baseline	1 (<1)	1 (<1)	0	0

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7.4.3 Other Hepatic Laboratory Abnormalities

Table 7.4.3 presents additional analyses for laboratory abnormalities that potentially reflect changes in hepatic function. In both populations, fewer on-treatment elevations of ALT > 2 × baseline or > 3 × baseline were observed in ETV-treated patients than in LVD-treated patients.

Table 7.4.3: Selected Treatment-Emergent Hepatic Laboratory Abnormalities, Nucleoside-Naive and LVD-Refractory Patients

	Nucleoside-Naive		LVD-Refractory	
Laboratory Test	**ETV 0.5 mg** N=679	**LVD 100 mg** N=668	**ETV 1.0 mg** N=183	**LVD 100 mg** N=190
ALT >2 × baseline	69/676 (10)	93/657 (14)	23/283 (13)	63/189 (33)
ALT >3 × baseline	32/676 (5)	52/657 (8)	8/183 (4)	31/189 (16)
ALT >2 × baseline *and* **Total Bilirubin** >2 × ULN and >2 × baseline	1/675 (<1)	3/656 (<1)	1/183 (<1)	2/189 (1)
Total Bilirubin ≥ 2.6 × ULN[a]	4/587 (<1)	6/612 (<1)	0/156	2/180 (1)
Albumin < 2.5 g/dL	4/674 (<1)	2/655 (<1)	0/181	3/187 (2)
Prothrombin Time > 1.5 × ULN[a]	4/463 (<1)	3/446 (<1)	2/147 (1)	4/152 (3)

[a] Grade 3 to 4 abnormalities for patients with a normal baseline value

7.5 Safety Cohort Analyses

Within the Safety Cohort database, the number of treated patients, the number of observations, and the duration of exposure are all greater for the any-ETV group than for the LVD group. Therefore, in order to make meaningful comparisons across treatment groups, the actual numbers of infrequent events must be analyzed as rates per treated individuals or incidence rates per unit of observation time (eg, per 1000 PY of observation). The observation time for these analyses includes both on-treatment and off-treatment follow-up time.

7.5.1 Deaths

A total of 15 deaths were reported in the Safety Cohort: nine occurred in ETV-treated patients and six occurred in LVD-treated patients. The rates of death across the two treatment groups were comparable whether calculated per number of patients treated or per unit of observation time: 0.6% and 4.4 per 1000 PY of observation, respectively, for ETV versus 0.7% and 5.1 per 1000 PY of observation, respectively, for LVD. Causes of death were generally consistent with chronic HBV infection or with an identified co-morbid disease. Four general categories can be identified among the observed causes of death. The single most frequent cause of death was malignancy (4 ETV; 1 LVD), and three of five events in this category were HCC (3 ETV; 0 LVD). The other categories are hepatic failure (2 ETV; 2 LVD), infection (2 ETV; 1 LVD), and cardiovascular/sudden death (1 ETV; 2 LVD). None of the events leading to death was considered by the investigator to be related to study drug.

Deaths occurring in one additional study outside the Safety Cohort (AI463048 in decompensated patients) are discussed in Section 7.6.2.

7.5.2 Monitoring for Malignant Neoplasms

The ETV clinical program monitored all reported events of neoplasms and analyses were performed using the Safety Cohort database. These events are of special interest in light of the findings from standard rodent carcinogenicity studies, in which lifetime administration of ETV was associated with increased incidences of benign and malignant neoplasms involving a variety of organ sites (Section 3.3.3).

In the Phase 2/3 clinical program for ETV, a total of 28 malignant neoplasms were reported in 26 patients from the Safety Cohort. The rates for patients having a new or recurrent diagnosis of a malignant neoplasm were comparable between the ETV and LVD groups, either by per number of patients treated or per PY of observation (Table 7.5.2A). The rates for malignant neoplasms in the Safety Cohort were also comparable to rates observed in BMS-sponsored epidemiologic studies in other cohorts of patients with chronic HBV infection: 6.5 per 1000 PY of observation in an HBV-infected cohort from Taiwan and 9.7 per 1000 PY of observation in an HBV-infected cohort from the US. Comparable malignancy rates between ETV- and LVD-treated patients from the Safety

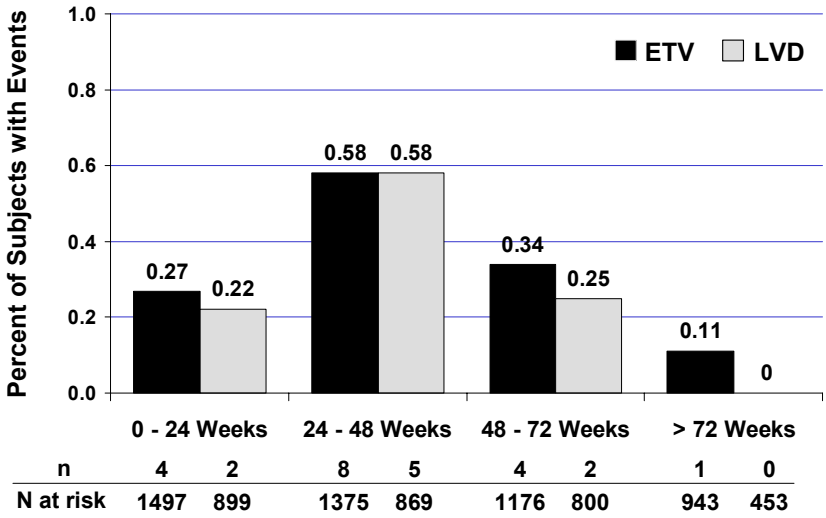
Cohort were observed for all sub-analyses performed: non-skin malignancies, HCC only, and non-skin, non-HCC malignancies.

Table 7.5.2A: Rates of Malignant Neoplasms, Safety Cohort

	Number (%) of Patients [Rate/1000 PY]	
Tumor Type	**ETV N = 1497**	**LVD N = 899**
All	17 (1.1%) [8.4]	9 (1.0%) [7.6]
All/Excluding Skin	14 (0.9%) [6.9]	8 (0.9%) [6.8]
HCC	7 (0.5%) [3.5]	4 (0.4%) [3.4]
Non-HCC/Excluding Skin	7 (0.5%) [3.5]	4 (0.4%) [3.4]

In addition, the distribution of new diagnoses of malignancy over time (Figure 7.5.2) demonstrated that the rates of diagnoses per incremental time period were comparable between the ETV and LVD groups. The greatest number of new diagnoses were made between Weeks 24 and 48, with an apparent leveling off for new diagnoses in the second year. This observation was consistent in both treatment groups and may reflect the on-study diagnosis of tumors that were latent at the time of enrollment.

Figure 7.5.2 Malignancy Diagnosis: Distribution over Time



A spectrum of malignant neoplasms has been observed in the ETV clinical program, with the most frequently reported event being HCC (Table 7.5.2B). As previously noted, HCC is an expected malignancy in a population with chronic HBV infection. The rates for HCC were comparable between the ETV and LVD groups (3.5 versus 3.4 per 1000 PY, respectively) (Table 7.5.2A).

The second most common malignancy type was skin cancer (basal and squamous cell types), which is common in the older population regardless of HBV status. All of the four patients in the Safety Cohort who developed new or recurrent skin cancer were over the age of 60 years at enrollment.

Eleven of the 26 patients with malignant neoplasms in the Safety Cohort had events of non-HCC, non-skin malignant neoplasms. Most of these neoplasms represent common tumor types observed in the general adult population, such as gastric, breast, and prostate cancers. The rate of non-HCC, non-skin malignant neoplasms was comparable between the two treatment groups (3.5 versus 3.4 per 1000 PY for ETV and LVD, respectively) (Table 7.5.2A).

Table 7.5.2B: Malignant Neoplasms, Safety Cohort

	Number (%) of Patients with Malignant Neoplasm		
Tumor Type	**ETV N = 1497**	**LVD N = 899**	**TOTAL N = 2396**
Any Malignant Neoplasm	17 (1)	9 (1)	26 (1)
Liver (HCC)	7 (<1)	4 (<1)	11 (<1)
Skin			
Basal Cell	3 (<1)	1 (<1)	4 (<1)
Squamous Cell	1 (<1)	0	1 (<1)
Prostate	2 (<1)	0	2 (<1)
Breast	1 (<1)	1 (<1)	2 (<1)
Gastric	1 (<1)	1 (<1)	2 (<1)
Lymphoma	1 (<1)	0	1 (<1)
Renal	1 (<1)	0	1 (<1)
Uterine	1 (<1)	0	1 (<1)
Carcinoma in Situ	0	1 (<1)	1 (<1)
Gastrointestinal Cancer Metastatic	0	1 (<1)	1 (<1)
Metastases to Central Nervous System	0	1 (<1)	1 (<1)

The assessment of malignancies in the ETV development program has two inherent limitations: the number of treated patients remains small relative to the desired sensitivity in detecting infrequent events such as malignancy, and the duration of observation remains short relative to the recognized latency periods for most human cancers. Nevertheless, a preliminary assessment based on the currently available data is that treatment with ETV is not associated with an increased risk for malignant neoplasms among individuals chronically infected with HBV.

7.5.3 Lactic Acidosis Signal Detection and Risk Assessment

Entecavir neither inhibits mitochondrial polymerase γ, nor adversely affects mitochondrial function in two other nonclinical assays. Clinical adverse events related to mitochondrial function and lactate metabolism would not be expected to be a frequent occurrence with ETV. This is recognized as a concern, however, for all nucleoside/nucleotide analogues, and an analysis for lactic acidosis syndrome (LAS) signal detection and risk assessment was conducted.

Serum lactate levels have poor predictive value for relevant clinical events and were not prospectively monitored in ETV studies.[24,25] Adverse events related to LAS may be reported less frequently in patients with HBV than in patients with HIV, where this is a well recognized syndrome. Underreporting bias cannot be ruled out. To assess LAS, the database for the Safety Cohort was retrospectively searched for adverse events that could be associated with LAS using 23 relevant event terms previously established in collaboration with the FDA for HIV studies. Of note, many of the terms capture non-specific liver disease. Twenty-two cases (ETV 11; LVD 10; placebo 1) were identified and reviewed to determine if case criteria for LAS were met using a definition derived from the HIV literature.[26] Sufficient data were available to make an assessment in 17 (77%) patients, of which 9 were ETV-treated; none of these 17 met the case criteria for LAS. Laboratory data were insufficient (no bicarbonate or lactate) for a full assessment in 5 patients (2 ETV, both 0.1 mg QD; 3 LVD). Both unclassifiable ETV patients experienced hepatic failure and death, but no relationship to ETV was identified on review of the two cases.

Although no events of LAS or symptomatic hyperlactatemia were identified in the Safety Cohort, one SAE of lactic acidosis was reported in a 19-year-old female from Study

AI463023, an ongoing study not included in the Safety Cohort. At study baseline, this patient had an unexplained low serum bicarbonate and anion gap. She developed LAS three months following initiation of ETV 0.5 mg, and lactic acidosis persisted more than 12 months following discontinuation of ETV. Although a pathologist determined that a bone marrow biopsy was suggestive of a myeloproliferative disorder, a hematologist concluded that the changes were nonspecific. Overall, the temporal pattern of this case suggests an etiology other than a drug-induced disruption of lactate metabolism.

7.6 Safety in Special Populations

7.6.1 Patients with HIV/HBV Coinfection (AI463038)

The safety of ETV in patients with HIV/HBV coinfection was assessed in 68 patients: 51 in the ETV group and 17 in the PBO group. In this population, the frequency of adverse events of any severity was comparable between ETV and PBO and was comparable to the frequency of on-treatment adverse events observed in other Phase 2/3 studies. No deaths were reported in this study. On-treatment ALT flares were infrequent, occurring in 4% of patients in the ETV group and none in the PBO group. No new safety issues associated with ETV treatment were identified in this patient population.

7.6.2 Patients with Decompensated Liver Disease (AI463048)

Preliminary data for the safety of ETV in patients with decompensated liver disease were assessed in 62 patients: 32 in the ETV group and 30 in the ADV group. In this population, the frequency of adverse events of any severity was comparable between ETV and ADV, and was comparable to the frequency of on-treatment adverse events observed in other Phase 2/3 studies.

There were 7 on-treatment deaths in this study: ETV 4 (13%), ADV 3 (10%). In addition, 3 deaths occurred during the screening period (2 due to liver failure, 1 due to sepsis); these pre-treatment deaths reflect the severity of illness in this decompensated population. The causes of death for the four ETV-treated patients were bacterial peritonitis, sepsis, sudden death/cardiovascular disease, and liver failure. Among ADV-treated patients, the causes of death were hypovolemic shock, liver failure, and hepatic encephalopathy. The number of deaths in this study is consistent with the severity of liver disease in this

decompensated cirrhotic population, for which the expected annual mortality rate is approximately 40%.[9]

In these decompensated patients, Grade 3 to 4 adverse events and SAEs were observed more frequently in the ETV group than in the ADV group (Grade 3 to 4 adverse events: ETV 53%, ADV 17%; SAEs: ETV 56%, ADV 20%). These two categories capture heavily overlapping events in this analysis. The imbalance in safety events may be related to an imbalance in the severity of hepatic decompensation at baseline, as assessed by the mean baseline Child-Pugh score (ETV 8.6, ADV 8.1) and the mean Mayo End Stage Liver Disease (MELD) score (ETV 15.8, ADV 13.2). Also, a greater number of ETV patients had a baseline Child-Pugh score ≥ 10, indicating that the majority of their hepatic functional capacity had been lost prior to treatment (ETV 9 patients; ADV 5 patients). There were no clusters of specific Grade 3 to 4 adverse events or SAEs that would suggest a safety signal for ETV. There were no reports of on-treatment ALT flares in this study.

7.7 Summary of Safety Evaluation

In clinical Phase 2/3 studies, approximately 1500 patients with chronic HBV infection were treated with ETV, and most received long-term therapy for at least 1 year. ETV was well tolerated and demonstrated a safety profile that was comparable to that of LVD and that did not vary with the dose used or the population treated. Treatment with ETV was associated with low rates of on- and post-treatment flares. Rates for diagnoses of new or recurrent malignancies were comparable for ETV- and LVD-treated patients, both overall and within relevant categories of tumor types. The consistency of results across diverse studies, across the two dose regimens, and across various demographic and disease subpopulations suggest a predictable safety profile that will be broadly applicable to the treated population anticipated in clinical practice.

8 PROPOSED PHARMACOVIGILANCE PLAN

Phase 2/3 clinical studies are designed to assess the efficacy and safety of an investigational drug within a relatively short period of 1 to 2 years. Postmarketing pharmacovigilance plans continue to assess the long-term benefits and risks of treatment in a larger patient population and under the conditions of usual clinical care.

Data from the ETV Safety Cohort do not demonstrate any increased risk of malignancy (either overall malignancies or HCC) associated with ETV treatment compared with LVD treatment, or compared with the background malignancy rates in chronically infected HBV patients. However, the clinical studies conducted to date on ETV do not contain sufficient numbers of patients or sufficient observation time to rule out an increased risk of an adverse event of low frequency and long latency, such as malignancy. Three ETV studies allow for ongoing long-term follow-up of ETV-treated patients (rollover treatment protocols AI463050 and AI463901 and the observational study AI463049). These studies will continue to provide sentinel assessments of the potential risk for malignant neoplasms and other long-term complications, as well as assessments of potential long-term benefit.

To address the long-term pharmacovigilance needs for ETV, BMS proposes to conduct a large simple safety study (AI463080) of ETV-eligible patients with chronic HBV infection, and to follow them for 5 years after the last patient has been enrolled (resulting in a maximum of 8 years of follow-up). Patients would be randomized at a 1:1 ratio to receive either ETV or a standard of care (other HBV nucleoside/nucleotide). Randomization would be stratified within the nucleoside/nucleotide-naive and the previously treated populations, with approximately 6250 patients per group. The study is powered to detect an increased relative risk of 1.4 for non-HCC malignancy and a decreased relative risk of 0.7 for HCC. This assumes a 20% loss to follow-up over 5 years with alpha (two-tailed) = 0.05 and power = 0.80. Previous studies have shown a background incidence rate of 400 malignancies/100,000 patient-years of follow-up for both non-HCC and HCC. Additional endpoints of this study will be overall mortality and progression of liver disease as measured by the frequency of liver transplantation and clinical events of hepatic decompensation.

In addition to this large simple safety study, the ongoing ETV clinical studies will undergo continuing review of adverse events and aggregate safety data. Post-approval pharmacovigilance activities will also include the following surveillance activities:

- All spontaneously reported serious and nonserious adverse events will be reviewed, with attention to adequacy of information, biological plausibility, and whether additional information is required to evaluate the event(s) in the context of the patient's other medical problems and concomitant medications. Where appropriate, such as for serious adverse events that have been identified for close scrutiny, BMS may directly contact the reporting health care professional to obtain follow-up

information. For selected events (HCC and other malignancies) on which periodic aggregate data analyses may be performed, a standardized set of queries will be used.

- BMS post-marketing review for safety signal detection will be performed on a periodic basis as one means of tracking malignancies in the post-approval period. Data review for frequency will be conducted, and findings will be compared with cumulative frequency. Published literature will also be searched for cases of malignancies in patients treated with ETV, and for malignancies occurring in patients treated with other nucleoside analogues.
- In addition, BMS will prepare periodic aggregate reports (US NDA Periodic Reports and Periodic Safety Update Reports). All relevant data will be reviewed by BMS and the malignancies identified will be described in the context of the total ETV experience.

9 BENEFIT VS RISK ASSESSMENT

9.1 Assessment of Risks

The overall clinical safety profile of ETV is benign and comparable to that for LVD. This observation was demonstrated consistently in a large and diverse development program. Regardless of the dose administered or the inherent risk characteristics of the population treated (nucleoside-naive and LVD-refractory; HBeAg-positive and HBeAg-negative; OLT recipient; and HBV/HIV co-infected), ETV treatment is associated with low rates of clinically important adverse events. Regardless of specific definition, the risk for hepatic flare is a universal safety concern when treating patients with chronic HBV infection. These events of acute hepatic inflammation can result in a rapid deterioration of liver function. In the ETV program, hepatic flares, as assessed by ALT and relevant clinical events, occur at low rates in ETV-treated patients, both on-treatment and during the first 6 months of post-treatment follow-up.

Given the favorable clinical safety experience over 1 to 2 years of ETV treatment in a broad range of patients with chronic HBV infection, the risk assessment for ETV is primarily concerned with the rodent tumor findings. The results of investigative studies suggest that lung tumors observed in mice at low exposure multiples result from unique effects of ETV on the mouse lung, whereas tumors in rodents occurring only at high doses/exposures may result from biochemical actions that are likely to demonstrate a biological threshold. ETV is a rodent carcinogen, and the investigative data do not definitively eliminate the risk to humans.

In assessing the clinical risk for patients with chronic HBV infection, it is acknowledged that the current human safety experience with ETV has certain limitations. The duration of observation is short relative to the recognized latency periods for most human cancers, and the number of treated patients limits the sensitivity to rule out risk for an infrequent event such as malignancy. Nevertheless, the available data, based on 1497 ETV patients treated for a mean of 60 weeks demonstrate that there is no early safety signal for an increased rate of cancers as a result of treatment with ETV. The ETV and LVD groups demonstrated comparable malignancy event rates, whether assessed as events per 1000 PY of observation or as events per patients exposed. The observed rates fall within the expected range for malignancies based on epidemiologic studies in populations with chronic HBV infection. As expected for the HBV-infected population, the most frequently reported individual tumor type in the ETV program was HCC, and rates for this tumor in the ETV development program are consistent with those identified in the literature.[3]

9.2 Assessment of Benefits

The clinical benefit of ETV derives from its potent and specific activity against HBV. The superiority of ETV over LVD, the nucleoside analogue most frequently used in the current treatment of chronic HBV infection, was established in multiple studies across various patient populations and across different endpoints. Assessment by histology provides a direct measure of clinically relevant improvements in liver inflammation, scarring, and cirrhosis. Correlation of cirrhosis with clinical decompensation and HCC is well established. In three large randomized, controlled, double-blind clinical trials, ETV demonstrated superiority in histologic improvement over LVD. For nucleoside-naive patients, the consistency across the HBeAg-positive and HBeAg-negative populations demonstrates the strength of these results. In LVD-refractory patients, ETV was superior to continued LVD for histologic improvement as well as for ALT and virologic responses.

The *in vitro* potency of ETV translates into virologic efficacy. Across ETV studies, the mean decreases in HBV DNA by PCR assay at Week 48 range from 5 to 7 $\log_{10}$ copies/mL. These decreases are greater than those for LVD. The potency of ETV, as reflected in the substantial $\log_{10}$ decreases in HBV DNA and in the high proportions of patients with HBV DNA < 400 copies/mL, is likely to contribute to the highly favorable

resistance profile in nucleoside-naive patients; effective suppression of the virus prevents replicative opportunities for the emergence of resistance.

The serologic response to ETV is consistent with that of other nucleoside antivirals, and non-inferiority to LVD was established in the ETV program. Lower serologic response rates in the LVD-refractory population are to be expected given the likelihood that the mean duration of prior LVD therapy (2.7 years) and the proportion with prior α-IFN experience (45%) select for a study population which may have a decreased ability to mount an immune-mediated seroconversion response. Also, given its favorable resistance profile, the full value of ETV may not become evident until additional long-term data are available.

Durability of treatment response after withdrawal of therapy provides another measure of long-term benefit. The performance of ETV is at least as good as that of LVD for nucleoside-naive, HBeAg positive patients. In nucleoside-naive HBeAg negative patients, ETV is observed to provide greater durability by bDNA and ALT evaluation, although almost all patients have recurrence of viremia by PCR. The resistance profile of ETV also contributes to the benefit conferred by adding ETV to the armamentarium of clinically available anti-HBV therapies. The antiviral efficacy of ETV, together with the absence of resistance after one year of treatment, makes this drug an ideal therapeutic agent for the nucleoside-naive population.

When ETV treatment follows prior use of LVD, the interaction between pre-existing LVD^R substitutions and the emergence of ETV resistance is complex. Clinical experience demonstrates that virologic rebounds due to ETV^R occur infrequently (1%) in the first year and are restricted to those patients harboring ETV^R substitutions at study entry. Data from clinical samples indicate that the 3 identified ETV^R substitutions do not appear in the nucleoside-naïve patients or in the absence of pre-existing LVD resistance. There is no apparent cross-resistance, in either direction, between ETV and ADV.

The tolerability of ETV and its clinical safety profile contribute to clinical benefit as the likelihood of discontinuation, interruption, or non-adherence to needed therapy is diminished. ETV is well tolerated without dose-associated symptoms and its safety profile is comparable to that for LVD, which is considered to be safe. To date, no specific organ toxicity was identified in the clinical experience. No lactic acidosis was found, as would be expected from the finding that ETV is not a substrate for mitochondrial

polymerase γ nor was any other hepatic or renal toxicity noted. Hepatic flares are the single most important disease-specific safety issue in chronic HBV infection, and ETV demonstrates a consistently low rate of ALT flares both during and especially post-treatment. Compared with LVD, ETV was consistently associated with fewer on-treatment ALT flares (approximately 50% those on LVD). Off-treatment ALT flares were infrequent (6% in nucleoside-naive and 5% in LVD-refractory patients), and none were associated with hepatic decompensation. The off-treatment flare data reflect the potency and clinical efficacy of ETV; sustained suppression of HBV DNA levels to undetectable or low levels results in prolonged viral control after drug is removed, and therefore in small numbers of rebound flare events. Thus, safety results from a diverse clinical program indicate that ETV has a predictable safety profile that will be broadly applicable to the treated population anticipated in clinical practice.

9.3 Benefit vs Risk Conclusions

In assessing the benefit vs risk of ETV, the substantial benefits of ETV represent an important treatment advance for patients with chronic HBV infection. The benefits of ETV compared with LVD demonstrated in the clinical program are substantial: superior virologic and histologic efficacy and a superior resistance profile. Also, the safety profile in patients followed in clinical studies for over 2 years, shows that ETV is well tolerated and lacks clinically important, drug-associated toxicity.

Nonclinical studies indicated that ETV is a rodent carcinogen. The subsequent investigative data submitted to the FDA CAC do not definitively eliminate a risk to humans. However, the hepatitis B virus is a human carcinogen that causes hepatocellular carcinoma[27]; chronic HBV infection is associated with a 30 × to 148 × higher relative risk compared with rates of this cancer in uninfected individuals.[3] Antiviral therapy with LVD prevents HCC,[4] a finding consistent with the known pathophysiology of the disease. There is a strong rationale to predict that the superiority of ETV over LVD in well established efficacy endpoints will lead to superior long-term benefit. This expected long-term benefit of ETV that results from the steep and durable HBV DNA reductions relative to LVD, and ETV's favorable resistance profile, should be considered when weighing overall benefit vs risk.

The benefit vs risk assessment for the treatment of chronic HBV infection with ETV will undergo periodic re-evaluation with expanding clinical experience, as is appropriate for all new medical therapies. The proposed post-marketing pharmacovigilance plan, which includes a large simple safety study of more than 5 years duration, will provide for continuing assessment of benefit vs risk; this ongoing assessment will be based on longer follow-up of more than 10,000 patients. The plan will effectively monitor the balance of potential risk for cancer with potential reductions in cirrhosis and HCC.

Overall, the proven benefit of ETV, when considering its potency and efficacy against the known carcinogen, HBV, supports its use for the proposed indication.

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Appendix: ETV Phase 2/3 Clinical Studies

Study/Phase/ Country	Study Design	Study Population	Dose and Duration	Treated Subjects
NDA STUDIES				
AI463022[a] (Pivotal)/ Phase 3/ Worldwide	Randomized, double-blind, double-dummy	Nucleoside-naive, $HBeAg^+$	• ETV 0.5 mg QD × 52 weeks vs LVD 100 mg QD × 52 weeks • Partial virologic responders may continue ETV 0.5 mg QD × 44 weeks vs LVD 100 mg QD × 44 weeks (total of 96 weeks of treatment)	ETV 0.5 mg: 354 LVD 100 mg: 355
AI463026[a] (Pivotal)/ Phase 3/ Worldwide	Randomized, double-blind, double-dummy	LVD-refractory, $HBeAg^+$	• ETV 1.0 mg QD × 52 weeks vs continued LVD 100 QD × 52 weeks • Partial virologic responders may continue ETV 1.0 mg QD × 44 weeks vs LVD 100 mg × 44 weeks (total of 96 weeks of treatment)	ETV 1.0 mg: 141 LVD 100 mg: 145
AI463027[a] (Pivotal)/ Phase 3/ Worldwide	Randomized, double-blind, double-dummy	Nucleoside-naive, $HBeAg^-$, $HBeAb^+$	• ETV 0.5 mg QD × 52 weeks vs LVD 100 mg QD × 52 weeks • Virologic-only responders may continue ETV 0.5 mg QD x 44 weeks vs LVD 100 mg QD × 44 weeks (total of 96 weeks of treatment)	ETV 0.5 mg: 325 LVD 100 mg: 313
AI463014[a] Phase 2/ Worldwide	Randomized, double-blind	LVD-refractory, $HBeAg^+$ or $HBeAg^-$, $HBeAb^+$	• 3 doses of ETV (0.1, 0.5 and 1.0 mg QD) vs continued LVD 100 mg QD for up to 76 weeks • (Subjects with <1 $\log_{10}$ HBV DNA reduction at Week 24 may discontinue dosing at Week 28) • Open-label ETV 1.0 mg QD until complete virologic response or study termination.	ETV 0.1 mg: 47 ETV 0.5 mg: 47 ETV 1.0 mg: 42 LVD mg: 45 ETV 1.0 mg (open label) : 27

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Appendix: ETV Phase 2/3 Clinical Studies

Study/Phase/ Country	Study Design	Study Population	Dose and Duration	Treated Subjects
AI463004[a] Phase 2/ Worldwide	Randomized, double-blind, dose-escalating	Nucleoside- naive and IFN/LVD- refractory, $HBeAg^+$ or $HBeAg^-$	ETV 0.05, 0.1, 0.5, 1.0 mg QD for 28 days vs PBO	ETV 0.05 mg: 8 ETV 0.1 mg: 9 ETV 0.5 mg: 9 ETV 1.0 mg: 8 PBO: 8
AI463005[a] Phase 2/ Worldwide	Randomized, double-blind, dose-ranging	Nucleoside- naive $HBeAg^+$ or $HBeAg^-$, $HBeAb^+$	• ETV 0.01, 0.1, 0.5 mg QD vs LVD 100 mg QD for 24 weeks. • Partial responders can receive open-label LVD for additional 24 weeks.	ETV 0.01 mg: 54 ETV 0.1 mg: 36 ETV 0.5 mg: 46 LVD 100 mg: 41
AI463007[a] Phase 2/ Worldwide	Open-label rollover study	Subjects who completed AI463004	ETV 0.1 mg QD x 24 weeks.	ETV 0.1 mg: 28
AI463012[a] Phase 2/ China	Randomized, double-blind, parallel group	Nucleoside- naïve, $HBeAg^+$ or $HBeAg^-$, $HBeAb^+$	• ETV 0.1 mg and 0.5 mg QD vs PBO QD for 28 days. • Open-label ETV 0.5 mg QD for 48 weeks	ETV 0.1 mg: 69 ETV 0.5 mg: 72 PBO: 71 ETV 0.5 mg (open label): 204
AI463015[a] Phase 2/ Worldwide	Open-label study of safety, PK and antiviral activity of ETV in liver transplant recipients	Liver transplant recipients who have reinfection with HBV despite LVD or HBIG post-transplant	• ETV 1.0 mg QD x 48 weeks • Extension phase for 48 weeks	ETV 1.0 mg: 9

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Appendix: ETV Phase 2/3 Clinical Studies

Study/Phase/ Country	Study Design	Study Population	Dose and Duration	Treated Subjects
AI463038/ Phase 2/ Worldwide	Randomized, double-blind, PBO-controlled; combined with LVD anti-retroviral regimen	HIV co-infected with LVD-refractory HBV	• ETV 1.0 mg QD vs PBO combined with LVD 300 mg daily × 24 weeks • open-label ETV 1.0 mg combined with LVD 300 mg daily × additional 24 weeks	ETV 1.0 mg: 51 PBO: 17
AI463048/ Worldwide	Open-label ETV vs ADV	Decompensated, HBeAg+ or HBeAg-	• ETV 1.0 mg QD × 52 weeks[b] • ADV 10 mg QD × 52 weeks[b]	ETV 1.0 mg: 32 ADV 10 mg: 30 (enrollment ongoing)
AI463056[a] Phase 2/ China	Randomized, double-blind, PBO-controlled	LVD-refractory, HBeAg$^+$ or HBeAg-	ETV 1.0 mg QD vs PBO × 12 weeks, followed by open-label ETV for 36 weeks	ETV 1.0 mg: 116 PBO: 29
OTHER STUDIES (unanalyzed; not included in the NDA submission)				
Phase 2				
AI463047/ Japan	Randomized, double-blind, double-dummy	Nucleoside-naive, HBeAg+ or HBeAg-	• ETV 0.01 mg QD × 24 weeks • ETV 0.1 mg QD × 24 weeks • ETV 0.5 mg QD × 24 weeks • LVD 100 mg QD × 24 weeks	ETV 0.01 mg ETV 0.1 mg ETV 0.5 mg LVD 100 mg Total N = 137[a]
AI463052/ Japan	Randomized, double-blind	LVD-refractory	• ETV 0.5 mg QD × 52 weeks • ETV 1.0 mg QD × 52 weeks	ETV 0.5 mg ETV 1.0 mg Total N = 84[a]
AI463053/ Japan	Randomized, double-blind	Nucleoside-naive	• ETV 0.1 mg QD × 52 weeks • ETV 0.5 mg QD × 52 weeks	ETV 0.1 mg ETV 0.5 mg Total N = 66[a]

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Appendix: ETV Phase 2/3 Clinical Studies

Study/Phase/ Country	Study Design	Study Population	Dose and Duration	Treated Subjects
AI463060/ Japan	Open-label rollover	Subjects from AI463047, AI463052, or AI463053	• ETV 0.5 mg QD long-term • ETV 1.0 mg QD long-term	ETV 0.5 mg ETV 1.0 mg Total N = 125 (enrollment ongoing)
AI463901/ Worldwide	Open-label rollover	Subjects from AI463005, AI463007, AI463014, AI463015, AI463022, AI463026, or AI463027	ETV 1.0 mg until complete response or up to 144 weeks (formerly a combination therapy of ETV 0.5 mg or 1.0 mg QD plus LVD 100 mg QD)	ETV 1.0 mg: 5 ETV+LVD: 854 (enrollment ongoing)
Phase 3				
AI463023/ China	Randomized, double-blind, double-dummy	Nucleoside-naive HBeAg+ or HBeAg-	• ETV 0.5 mg QD × 52 weeks vs LVD 100 mg QD × 52 weeks • Partial responders may continue blinded study drug for up to 96 weeks	ETV 0.5 mg LVD 100 mg Total N = 519[c]
AI463049/ Worldwide	Observational, 5-year follow-up	Any subject enrolled in Phase 3 or rollover studies	Not applicable	426 as of 14Oct2004 (Observation only; enrollment ongoing)
AI463050[d]/ China	Open-label rollover	Subjects from AI463012, AI463023, or AI463056	• ETV 0.5 mg QD long term • ETV 1.0 mg QD long term	ETV0.5 mg ETV 1.0 mg Total N = 55 (enrollment ongoing)

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Appendix: ETV Phase 2/3 Clinical Studies

Study/Phase/ Country	Study Design	Study Population	Dose and Duration	Treated Subjects
AI463900/ Worldwide	Open-label, early access	Subjects 1)who failed or were intolerant of prior interferon, LVD, or ADV (where marketed) 2) for whom use of these agents is contraindicated 3) rollover from Phase 2/3 studies	ETV 1.0 mg QD × 96 weeks	ETV 1.0 mg: 36 (enrollment ongoing)

[a] Study remains blinded.

[b] Or up to 96 weeks or until a complete virologic response is achieved

[c] 258 ETV; 261 LVD.

[d] First subject enrolled after the data cut-off for the NDA submissions.

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