FDA Advisory Committee Briefing Document

Adefovir Dipivoxil
For the Treatment of Chronic Hepatitis B

NDA 21-449

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GLOSSARY OF ABBREVIATIONS

ADV	Adefovir dipivoxil
ADME	absorption, distribution, metabolism, excretion
ALT (SGPT)	alanine aminotransferase
anti-HBe	antibody to hepatitis B envelope antigen (HBeAg)
AST (SGOT)	aspartate aminotransferase
AUC	area under the (time–plasma concentration) curve
$AUC_{0-\tau}$	area under the plasma concentration versus time over the dosing interval
$AUC_{0-\infty}$	area under the plasma concentration versus time from time zero and extrapolated to infinite time
CI	confidence interval
CL_f	apparent clearance of drug
CL_{renal}	renal clearance
C_{max}	maximum plasma concentration
dATP	deoxyadenosine triphosphate
dL	deciliter
DAVG	difference between time-weighted average post baseline and baseline
DHBV	duck hepatitis B virus
DNA	deoxyribonucleic acid
ESRD	end stage renal disease
FDA	Food and Drug Administration
FIAU	fialuridine
FIV	feline immunodeficiency virus
G/L	grams per liter
HAI	histologic activity index
HBIg	hepatitis B immune globulin
HBeAg	hepatitis b envelope antigen
HBsAg	hepatitis b surface antigen
HBsAb	hepatitis b surface antibody
HBV	hepatitis b virus
HCC	hepatocellar carcinoma
HCMV	human cytomegalovirus
HCV	hepatitis C virus
HDV	hepatitis D virus
HHV	human herpes virus
HIV	human immunodeficiency virus
hr	hour
HSV	herpes simplex virus
IC_{50}	concentration that inhibits 50% of viral infection

GLOSSARY OF ABBREVIATIONS (CONTINUED)

IFN-α	interferon alpha-2b
ISS	Integrated Summary of Safety
ITT	intent-to-treat (population)
IU/L	international units per liter
IVRS	interactive voice recognition system
Ki	kinetic inhibition constant
KM	Kaplan-Meier
LAM	lamivudine
LLQ	lower limit of quantitation
MEL	minimum effect level
mg	milligram(s)
mg/dL	milligrams per deciliter
mg/kg	milligrams per kilogram
mL	milliliter(s)
MTD	maximum tolerated dose
N or n	number
NDA	New Drug Application
ng	nanogram
NOAEL	no adverse effect level
NOEL	no observable effect level
PCR	polymerase chain reaction
pol/RT	polymerase/reverse transcriptase
RPTEC	renal proximal tubule epithelial cells
RT	reverse transcriptase
SAE	serious adverse event
SD	standard deviation
SKMCs	skeletal muscle cells
T_{max}	time to maximum plasma concentration
$t_{1/2}$	elimination half-life
µg/L	micrograms per liter
µg•hr/L	micrograms per hour per liter
µg/mL	micrograms per milliliter
µM	micromole
ULN	upper limit of the normal range
µmol/L	micromoles per liter
WHV	woodchuck hepatitis virus
YMDD	tyrosine-methionine-asparatate-aspartate

1. SUMMARY

Chronic hepatitis B is one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma. It is associated with high morbidity and mortality and remains a significant healthcare issue. Licensed treatments such as interferon-α and lamivudine provide therapeutic options for the treatment of chronic hepatitis B. However, both agents are limited therapeutically; in the case of interferon-α principally because of its tolerability and limited efficacy in many subpopulations and for lamivudine because of the emergence of resistance. New therapies that are well tolerated and not prone to resistance development are needed for treatment of patients with chronic hepatitis B to provide effective and sustained suppression of viral replication, and improvement of liver histology, with the long-term goal of preventing progression of liver disease.

Adefovir dipivoxil is an oral prodrug of adefovir that has been developed by Gilead Sciences for use in the treatment of chronic hepatitis B. Adefovir is a member of a new class of antiviral compounds known as nucleotide (nucleoside monophosphate) analogues that have activity against hepadnaviruses, retroviruses, and herpes viruses. The active intracellular moiety of adefovir, adefovir diphosphate, acts as a competitive inhibitor and chain-terminator of hepatitis B virus (HBV) replication mediated by HBV DNA polymerase. *In vitro* and *in vivo* evidence have demonstrated that adefovir is a potent inhibitor of HBV replication with activity against wild type and nucleoside-resistant strains of HBV.

The clinical development program of oral adefovir dipivoxil in chronic hepatitis B was initiated in 1995, leading to submission of a New Drug Application (NDA) in March 2002 (NDA 21-449). The NDA provided the results of a comprehensive program of preclinical investigations and clinical trials to determine the therapeutic benefits of adefovir dipivoxil in the treatment of chronic hepatitis B in adults. The clinical development program evaluated the efficacy and safety of adefovir dipivoxil 10 mg (the recommended dose for clinical use) in a number of different chronic hepatitis B populations. These populations include chronic hepatitis B patients with compensated liver disease, both HBeAg positive and HBeAg negative (presumed precore mutant), chronic hepatitis B patients with lamivudine-resistant HBV including patients with compensated and decompensated liver disease, patients pre- and post-liver transplantation as well as patients co-infected with HIV. The clinical program is ongoing and continues to provide long-term efficacy, safety and resistance data in these patient populations with chronic hepatitis B.

Through December 31, 2001 (safety cutoff for NDA submission) 1,517 patients with chronic hepatitis B, non-HBV infected patients, and healthy volunteers had received adefovir dipivoxil at the recommended dose of 10 mg daily for varying lengths of exposure in studies in the clinical development program. The safety database described in the Integrated Summary of Safety (ISS) reflected clinical experience in 523 patients with chronic hepatitis B who have received treatment with adefovir dipivoxil 10 mg daily for ≥ 48 weeks, including 316 patients treated for ≥ 72 weeks and 70 patients treated for ≥ 96 weeks. A summary of safety data from the earlier HIV program specifically related to elevations of serum creatinine

and reductions in serum phosphorus seen at higher doses was also included in the ISS. As of February 28, 2002 (safety cutoff for NDA 21-449 Safety Update), the total number of patients exposed to adefovir dipivoxil 10 mg, in the pivotal studies, GS-98-437 and GS-98-438 and in a supportive study in patients pre- and post-liver transplantation had reached 816 in the safety update which included 578 patients with chronic hepatitis B treated for ≥ 48 weeks, 420 patients treated for ≥ 72 weeks, and 256 patients treated for ≥ 96 weeks. The pivotal studies remain ongoing.

The results of the clinical program to date demonstrate that adefovir dipivoxil 10 mg provides significant histological, antiviral, clinical and immunological benefits for patients with chronic hepatitis B. These effects have been demonstrated in patients with HBeAg positive and HBeAg negative (presumed precore mutant) chronic hepatitis B and with compensated liver disease treated for up to 48 weeks in placebo-controlled clinical trials. Adefovir dipivoxil 10 mg has also been shown to provide similar antiviral and clinical benefits for patients who have failed lamivudine therapy, including pre- and post-liver transplantation patients, patients with compensated or decompensated liver disease and patients with chronic hepatitis B co-infected with HIV.

Adefovir dipivoxil has been shown to have a unique resistance profile, with no evidence of adefovir-associated resistance mutations identified to date following extensive prospective resistance monitoring in the phase 3 placebo-controlled clinical studies up to 48 weeks, and for treatment periods as long as 136 weeks in open-label phase 2 studies. The lack of resistance to date is a key distinguishing feature of adefovir dipivoxil therapy compared with lamivudine therapy.

All available clinical data from a substantial population of patients with chronic hepatitis B and compensated liver disease demonstrate a favorable safety and tolerability profile for adefovir dipivoxil 10 mg once daily with no evidence of any clinically significant toxicity. In liver transplantation patients with lamivudine-resistant HBV (both waitlisted and post-transplantation) with chronic hepatitis B treated with adefovir dipivoxil 10 mg, a highly favorable risk-benefit profile is demonstrated for patients with limited alternative treatment options who are at high risk of disease progression and/or liver graft loss and death if recurrent hepatitis B is not controlled. In these patients, adefovir dipivoxil 10 mg meets an urgent unmet medical need and presents a life-saving treatment option. Routine monitoring of serum creatinine is recommended in patients with history of, or at risk for, renal dysfunction. Following pharmacokinetic evaluations in patients with renal impairment, it has been determined that it is necessary to alter dose interval in patients with creatinine clearance < 50 mL/min, if renal function changes during treatment dose interval adjustment is required according to dosing guidelines. There are no notable accompanying changes in serum phosphorus that warrant routine monitoring of serum phosphorus during treatment with adefovir dipivoxil. Since evidence of exacerbations of hepatitis has been observed in some patients after discontinuation of adefovir dipivoxil 10 mg, patients should be monitored post-treatment for signs of reactivation of chronic hepatitis B.

2. INTRODUCTION AND THERAPEUTIC RATIONALE

Adefovir dipivoxil is an oral prodrug of adefovir, a phosphonate nucleotide analog of adenosine monophosphate that possesses potent *in vitro* activity against hepadnaviruses, retroviruses and herpesviruses. The active intracellular metabolite of adefovir is adefovir diphosphate, which selectively inhibits HBV DNA polymerases.

Adefovir is not well absorbed in the intestine because of the presence of the negatively charged phosphonate group. Therefore a prodrug, adefovir dipivoxil, was developed to improve oral bioavailability. The dipivoxil prodrug moiety is rapidly cleaved by esterases to liberate free adefovir into the portal and systemic circulation. Other identified metabolites include pivalic acid and formaldehyde.

Therapeutic Rationale

Chronic hepatitis B is a serious global healthcare problem and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma. Current estimates suggest that approximately 400 million people worldwide, and approximately 1.25 million people in the US, are chronically infected with HBV.[1-3] Between one quarter and one third of people with chronic hepatitis B will go on to develop progressive liver disease; approximately one million die annually, making chronic hepatitis B the tenth leading cause of death worldwide.[1-3] Despite the availability of HBV vaccine programs in many countries, new hepatitis B infections are still common; for example, approximately 80,000 people in the United States become acutely infected each year.

Following acute hepatitis B infection, approximately 5% of adults and 80% to 90% of children fail to produce an adequate immune response to HBV and become chronic carriers of the virus. The diagnosis of chronic HBV infection is based on serological findings, specifically, the continued presence of the HBV surface antigen (HBsAg), high levels of HBV DNA and usually the presence of hepatitis B envelope antigen (HBeAg). Sustained disease remission is characterized by loss of HBeAg and development of antibody to HBeAg (anti-HBe).

In Southern Europe and Asia, HBeAg negative (i.e. HBeAg negative/anti-HBe positive/HBV DNA positive) chronic hepatitis B, also referred to as presumed precore mutant chronic hepatitis B, is particularly common. This type of chronic hepatitis B exists worldwide (accounting for 7% to 30% of infection depending on geographical region) and is generally due to the selection of an important variant form of HBV harboring a mutation in the precore region of the hepatitis B genome that prevents the virus from producing HBeAg. Chronic hepatitis B as a result of HBeAg-negative HBV variants has a more variable disease course than HBeAg positive chronic hepatitis B, and is associated with wide fluctuations over time in viral replication and disease activity, with recurrent relapses. In addition, a much lower rate of spontaneous remission is seen. The proportion of chronic liver disease associated with precore mutant HBV is increasing, particularly in Southern Europe and Asia. In most recent data from the US, the prevalence of HBeAg negative disease is increasing. Therefore,

effective treatment of both HBeAg positive and HBeAg negative chronic hepatitis B is an important aspect in the management of chronic hepatitis B and its associated complications.

The immediate aims of treatment in chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease to prevent progression to advanced hepatic fibrosis and cirrhosis, and other long term sequelae. In the US, two treatments for chronic hepatitis B are currently available: interferon-α, a parentally administered cytokine immune modulator with antiviral activity, and lamivudine, an oral nucleoside analog that inhibits HBV DNA synthesis by chain termination. Despite the efficacy of these agents in patients with chronic hepatitis B, important limitations to their use remain.

Interferon-α is administered over a 16 week period by subcutaneous injection three times weekly to enhance the immune response and induce HBeAg and possible HBsAg seroconversion. Efficacy is variable with rates of HBeAg loss ranging from 15% to 33%.[4-6] Interferon-α is used to treat patients with HBeAg positive chronic hepatitis B and compensated liver disease. The use of interferon-α is of limited efficacy in patients with HBeAg negative chronic hepatitis B (i.e., HBeAg-/anti-HBe+/HBV DNA+, also described as presumed precore mutant) or in patients who are immunocompromised (HIV positive patients or liver transplantation recipients). Interferon-α is contraindicated in patients with decompensated liver disease. Additional limitations of interferon-α include a range of clinical adverse effects and laboratory abnormalities that frequently require dose reduction, interruption, or discontinuation.[7]

Lamivudine has been shown to improve liver histology, reduce serum HBV DNA levels, and normalize serum transaminases in patients with HBeAg positive chronic hepatitis B.[6, 8-10] In placebo controlled clinical trials, histological responses were observed in 52% to 56% of lamivudine recipients and 23% to 25% of placebo recipients after one year of treatment. Lamivudine was also associated with a significant reduction of serum HBV DNA concentrations.[11] Lamivudine is well tolerated, but the emergence of lamivudine-resistant (YMDD) HBV mutants is associated with loss of clinical response and progressive liver disease limiting the long-term benefit to patients. As illustrated below, YMDD HBV mutants have been reported in a significant proportion of patients treated with lamivudine; in 14% to 32% after one year of therapy increasing to up to 69% in chronic hepatitis B patients after 5 years.[8, 9, 11-14] In patients with HIV co-infection, the estimated incidence of lamivudine-resistant HBV reaches 50% after 2 years and up to 91% after 4 years of lamivudine therapy.[15]

Patients with liver failure due to chronic hepatitis B represent a significant population of liver transplantation recipients. Patients undergoing liver transplantation for chronic hepatitis B disease have historically done poorly, largely due to the development of recurrent infection post-transplantation characterized by high levels of HBV replication. Reinfection post-transplantation has severe consequences in immunosuppressed liver transplantation patients; 1 and 5 year survival rates of 73% and 44%, respectively, are reported for this group of patients.[16] Current treatment strategies focus on preventing reinfection of the graft with high-dose hepatitis B immune globulin (HBIg), or limiting the effects of viral replication post-transplantation with lamivudine. As a result, survival rates post-transplantation in

chronic hepatitis B patients following the availability and widespread use of these agents have improved in recent reports (approximately 88% to 92% after two years).[17] However, HBIg prophylaxis is expensive, has to be given parenterally and indefinitely, and cannot be used to actively treat recurrent HBV infection after transplantation. HBIg prophylaxis has also led to the selection of S gene escape mutations.[18] With respect to lamivudine, the improved survival rate is unlikely to be sustained in the long-term due to the frequent emergence of resistance in this immunosuppressed population.[19, 20] Interferon-α therapy has limited utility in the post-transplantation setting because of the risk of graft rejection.

Because each of the currently available agents for the treatment of chronic hepatitis B are limited therapeutically, there is a need for novel, safe and well-tolerated agents for the treatment of chronic hepatitis B, which provide clinical efficacy and sustained suppression of HBV replication and present a higher threshold for emergence of resistance.

Rationale for Adefovir Dipivoxil in the Treatment of Chronic Hepatitis B

The preclinical evaluation of adefovir dipivoxil demonstrates favorable properties that point to its potential as an effective agent for the treatment of chronic hepatitis B.

The active intracellular metabolite, adefovir diphosphate, selectively inhibits HBV DNA polymerase (K_i value of 0.1 μM) at a concentration 12-, 700-, and 10-fold lower than needed to inhibit human DNA polymerases α, β, and γ, respectively.

In cell culture models, adefovir demonstrated potent antiviral activity against HBV and a lack of cross-resistance against the lamivudine-resistant strains of HBV tested, i.e., L528M, M552V, M522I, and L528M/M552V. In enzymatic assay models of viral replication, HBV encoding these lamivudine resistance mutations is 8 to 25-fold less sensitive to lamivudine than wild type virus. Results are shown in Table 1. These mutants all remained sensitive to adefovir. The *in vitro* findings were further confirmed by animal studies that demonstrated potent activity in animal hepadnavirus models including duck HBV infection, woodchuck hepatitis virus infection and in transgenic mice expressing HBV. Finally, adefovir has a long intracellular half-life of approximately 12 to 36 hours, which makes it suitable for once daily oral dosing.

Table 1. Antiviral Activity of Adefovir and Cross-Resistance of Emtricitabine Versus HBV Encoding Known Lamivudine Resistance Mutations

	Fold Resistance[1]					
	Adefovir		Lamivudine		Emtricitabine	
Mutations/Strains	Cell Culture[2]	Enzymatic[3]	Cell Culture[2]	Enzymatic[3]	Cell Culture[2]	Enzymatic[3]
Wild-type	1.0	1.0	1.0	1.0	1.0	1.0
L528M	0.4 – 1.1	2.3	2.5 - 18	2.6	11	2.6
M552I	0.7 – 7.8	1.3	380 – > 10,000	8.0	> 42	20.3
M552V	0.5 – 8.4	2.2	22 - 221	19.6	230	15.3
L528M/M552V	0.4 – 3.8	0.79	312 – > 10,000	25.2	> 42	13.1

1 Fold of resistance is defined as the ratio of K_i (mutant)/K_i (wild type) or IC_{50} (mutant)/IC_{50} (wild type). Drug resistance phenotype is defined as a ≥ 5-fold increase in this factor in the enzymatic assay. In cell culture, the phenotype resistance has been defined as > 10 increase.

2 Data from references: [21-28]

3 Data from reference: [29]

3. PRECLINICAL DEVELOPMENT

The key findings of the pharmacology, virology, ADME, and toxicology evaluation of adefovir dipivoxil are:

- Adefovir has potent anti-HBV activity *in vitro* and *in vivo* against wild-type and drug-resistant mutants of hepatitis B virus. There was no evidence for adefovir-related mitochondrial toxicity from *in vitro* or *in vivo* studies.

- In *in vitro* or *in vivo* studies, there was no evidence for adefovir-related mitochondrial toxicity. Adefovir is not a substrate or inhibitor of cytochrome P450.

- Adefovir is excreted unchanged in the urine in all species.

- Renal toxicity was the major target organ toxicity identified in all species evaluated. The renal effects occur in a predictable, dose-related manner and predict the dose-limiting toxicity in humans.

- Gastrointestinal toxicity in animals appears to be associated with high dose local intestinal exposure and should not pose a safety concern in humans at the recommended therapeutic dose.

- Modest elevations in liver transaminases were seen in rats and monkeys. Histological changes were seen in mice at high doses providing a large margin of safety relative to the human dose.

- Toxic effects on the hematopoietic system occurred only at relatively high doses of adefovir administered parenterally and have a large margin of safety relative to the human clinical dose.

- There were no adverse reproductive effects in male or female animals and no fetal developmental/teratogenic effects identified in rats or rabbits treated with adefovir dipivoxil. When administered at maternally toxic doses in rats, intravenous adefovir was teratogenic. Since there are no studies in pregnant women, adefovir should be used in pregnancy only if clearly needed, and after careful consideration of risks and benefits.

- Adefovir dipivoxil was not carcinogenic in chronic rat and mouse studies.

A more detailed summary of the preclinical findings, including the results of the toxicological evaluation, is provided in Appendix 1.

4. CLINICAL DEVELOPMENT PROGRAM

The clinical program of adefovir dipivoxil 10 mg in chronic hepatitis B comprises a range of registrational clinical trials designed to determine the efficacy and safety of adefovir dipivoxil 10 mg daily in patients with chronic hepatitis B. In conjunction with the clinical studies, virology resistance surveillance studies were prospectively designed and conducted to allow thorough investigation of the potential for the development of resistance to adefovir. A summary of the studies contributing data to the current assessment is provided in Table 3. A more detailed summary of the ongoing clinical program of adefovir dipivoxil in chronic hepatitis B is provided in Appendix 7.

The clinical development program includes two ongoing, phase 3 studies of adefovir dipivoxil 10 mg conducted in patients with chronic hepatitis B with compensated liver disease and evidence of HBV replication:

- GS-98-437 (study 437), a randomized, placebo-controlled study conducted in patients with wild type, HBeAg positive chronic hepatitis B.

- GS-98-438 (study 438), a randomized, placebo-controlled study conducted in patients with HBeAg negative (presumed precore mutant) chronic hepatitis B.

Results of four ongoing supportive clinical studies are reported in which adefovir dipivoxil 10 mg is administered to populations of patients with chronic hepatitis B and diminished therapeutic response to lamivudine. These studies include:

- GS-98-435 (study 435): A phase 3, open-label study in patients who received liver transplantation or are waitlisted for liver transplantation. At the time of NDA clinical data cutoff, data for the post-liver transplantation cohort were available for reporting. The Safety Update Report has provided data for patients waitlisted for transplantation to allow assessment of risk-benefit for this cohort.

- GS-00-461 (study 461): An active-controlled study of the combination of adefovir dipivoxil and lamivudine, as well as adefovir dipivoxil alone and lamivudine alone, in patients with HBeAg positive compensated liver disease.

- GS-99-465 (study 465): A collaborative, randomized placebo-controlled (cohort A) and open-label (cohort B) study sponsored by GlaxoSmithKline evaluating the addition of adefovir dipivoxil 10 mg to lamivudine therapy in subjects with chronic hepatitis B and with compensated (cohort A) or decompensated (cohort B) liver disease. Available data for the decompensated patient cohort receiving open-label adefovir dipivoxil in combination with lamivudine are reported.

- GS-00-460i (study 460i): A physician-sponsored open-label study in chronic hepatitis B patients co-infected with HIV and with compensated liver disease.

In addition, the clinical program includes four phase 1 and phase 2, dose-ranging studies (studies GS-94-404, GS-96-412 and GS-96-413 and the extension/maintenance study of GS-96-412), and a further open-label compassionate use study in patients with end-stage liver disease who were failing lamivudine (study GS-98-451i).

The results of a comprehensive program of clinical pharmacokinetic studies were also reported in the NDA including single and multiple dosing in patients with chronic hepatitis B, studies in non-HBV-infected subjects with impaired renal function and impaired hepatic function, and studies in healthy volunteers to investigate possible drug interactions and food effect. A more detailed summary of the pharmacokinetic studies is provided in Appendix 2.

Single and multiple oral administrations of adefovir dipivoxil 10 mg to patients with chronic hepatitis B resulted in a predictable concentration time profile and pharmacokinetics that were similar to those observed in healthy subjects. Maximum observed plasma adefovir concentrations (C_{max}) were 17.5 to 21.3 ng/mL were rapidly achieved (T_{max} = 0.76 to 1.75 hr) then declined with a long terminal elimination half-life, allowing for once daily dosing (study GS-00-472).

The oral bioavailability of adefovir from a 10 mg dose of adefovir dipivoxil 10 mg was estimated to be approximately 59 percent (study GS-00-472). Plasma adefovir pharmacokinetics were unaffected by the administration of food (study GS-00-476).

Adefovir renal clearance was approximately twice the calculated creatinine clearance indicating tubular secretion is an important contributor to the elimination of adefovir. The amount of adefovir recovered in the urine approximated estimated oral bioavailability (studies GS-00-472 and GS-00-475).

The pharmacokinetics were unaltered by concomitant administration of a variety of medications that are expected to be taken by patients with chronic hepatitis B, including lamivudine, acetaminophen, and trimethoprim sulfamethoxazole. Increased exposure to adefovir was observed when co-administered with the highest recommended clinical dose of ibuprofen but this was not of sufficient magnitude to warrant a change in the dose regimen of adefovir dipivoxil (study GS-00-475).

No substantial alterations in adefovir systemic exposure were observed in the presence of mild renal impairment ($CL_{cr} \geq 50$ mL/min). Subjects with moderate or severe renal impairment ($CL_{cr} < 50$ mL/min or those with end stage renal disease (ESRD) requiring hemodialysis exhibited higher systemic exposures to adefovir that necessitate dose-interval adjustments (Table 2). Hemodialysis effectively removed adefovir from the systemic circulation.

Table 2. Recommendations for Dose Interval Modification of Adefovir Dipivoxil in Renal Impairment

Calculated Creatinine Clearance (mL/min)				Requiring Hemodialysis
≥ 50	20–49	10–19	< 10	
Normal Dosage Regimen i.e., 10 mg every 24 hours	10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days	10 mg every 7 days post hemodialysis

No substantial alterations in the pharmacokinetics of adefovir were observed in subjects with moderate or severe hepatic impairment (study GS-00-474). No dose adjustment of adefovir dipivoxil 10 mg is recommended in patients with compromised liver function.

Substantial differences in steady state pharmacokinetics with respect to demographic factors (HBV infection, gender, race, age and weight) were not apparent. There are limited pharmacokinetic data in geriatric subjects. Differences in adefovir pharmacokinetics in the elderly may occur due to changing and/or diminished renal function or other physiologic changes in the elderly.

Table 3. Summary of Adefovir Dipivoxil Studies Included in the NDA

Study No.	Patient Population	Dose (s) (mg/day)	Total Enrolled	Location	Status (as of June 2002)
Phase 3 Studies in Chronic Hepatitis B Patients					
437	Chronic hepatitis B (HBeAg positive)	10, 30 mg	515	US, Europe, Canada, Australia, Asia	Year 1 complete Blinded Year 2 stopped. Patients rolled into studies 480/481 (see Appendix 7) or 437 Long-Term Safety and Efficacy (437 LTSE)
438	Chronic hepatitis B (presumed precore mutant)	10 mg	185	Europe, Canada, Australia, Asia, Israel	Year 1 complete Year 2 ongoing. On completion, patients rolled into Study 480 or 438 LTSE)
435	Chronic hepatitis B /lamivudine resistance / post transplantation or waitlisted for transplantation	10 mg	324*	US, Europe, Canada, Hong Kong, Australia	Ongoing enrollment
460i	Chronic hepatitis B /HIV co-infection /lamivudine resistance	10 mg	35	France	Enrollment complete Year 1 complete Year 2 complete Year 3 ongoing
461	Chronic hepatitis B /lamivudine resistance/ compensated liver disease	10 mg	59	US, Europe, Australia, Canada	Enrollment complete Week 16 data in NDA Week 48 now completed
465	Chronic hepatitis B (HBeAg+ and HBeAg- patients) /lamivudine resistance Stratum A-Controlled Stratum B-open-label (decompensated)	10 mg	135**	US, Canada, Europe and Asia	Enrollment complete Year 1 complete Year 2 ongoing (only open-label Stratum B to week 24 reported in NDA)***
Phase 1/Phase 2 Studies in Chronic HBV-Infected Patients					
404	Chronic hepatitis B /elevated ALT	Initial: 125 mg Maint. (60 and 120 mg)	20 (15)	UK	Initial and maintenance phases complete
412	Chronic hepatitis B /elevated ALT	5, 30, 60 mg	63	US, UK, Australia, Canada	Initial and extension phases complete.
413	Chronic hepatitis B /normal ALT	30 mg	15	US, UK, Australia, Canada	Complete
412 ext/ maint	Chronic hepatitis B	30 mg reduced to 10 mg	39	US, UK, Canada	Ongoing
Open-Label Safety					
451i	Chronic hepatitis B /pre or post liver transplant/ failing therapies	5-30 mg	26	US, UK, Germany, Switzerland, Italy, Canada, Australia, Asia,	Ongoing

* Data for 131 post-liver transplantation patients were reported in the NDA. In the Safety Update Report, data for a total of 324 patients are reported (post-transplantation, cohort A, n = 196; waitlisted for transplantation, cohort B, n = 128).

** Patients enrolled include 95 patients with compensated liver disease and 40 patients with decompensated liver disease. Data from 40 patients with decompensated disease in the open-label arm are reported.

*** Data from week 48 now available for both Stratum A and Stratum B.

5. CLINICAL EFFICACY

5.1. Phase 1/Phase 2 Studies

Four phase 1 and phase 2 studies (studies 404, 412, 412 extension and 413) were conducted to confirm the *in vitro* findings of anti-HBV activity and to identify the recommended dose for clinical use. These studies, conducted in both HBeAg positive and HBeAg negative patients with chronic hepatitis B, demonstrated that adefovir dipivoxil is a potent inhibitor of hepatitis B virus replication associated with HBeAg seroconversion and ALT normalization. The principal efficacy findings of these studies are summarized in Table 4.

In chronic hepatitis B patients, statistically significant decreases in serum HBV DNA levels were demonstrated within the first week of treatment, and were maintained for periods of treatment up to 136 weeks. After 12 weeks of treatment, adefovir dipivoxil at doses of 30 mg and 60 mg once daily reduced serum HBV DNA levels by approximately 4 $\log_{10}$ copies/mL (determined by Roche PCR, LLQ < 400 copies/mL) from baseline (study 412).

Clinical evidence of viral resistance to adefovir dipivoxil was not observed in any of the four studies. Virology substudies were also performed in conjunction with the phase 1 and phase 2 clinical studies as part of a wider prospective program for resistance surveillance. The results of the HBV genotypic and phenotypic analyses demonstrated that adefovir dipivoxil (5-125 mg daily) did not lead to the emergence of adefovir-associated resistance mutations of HBV, including 27 patients treated initially with adefovir dipivoxil 30 mg, and subsequently with 10 mg daily for up to 136 weeks.

Rationale for Dose Selection for Phase 3 Program

Adefovir dipivoxil 10 mg once daily was selected as the therapeutic dose for treatment of chronic hepatitis B on the basis of risk benefit considerations for this indication. The antiviral response seen in study 412 indicated a suboptimal antiviral effect with 5 mg daily and maximal and similar reductions in serum HBV DNA levels with doses of 30 mg and above (study 412). On the basis of these data, 30 mg and a proposed lower dose of 10 mg daily based on mathematical modelling were chosen for phase 3 evaluation. Before the commencement of the second pivotal study (study 438), long-term safety data from study 412 indicated that daily dosing with 30 mg daily beyond 20 weeks was associated with the emergence of mild nephrotoxicity that was reversible upon discontinuation of drug. This observation with the 30 mg dose was later confirmed by safety data from study 437 (see Appendix 3). Since patients who do not undergo HBeAg seroconversion after 48 weeks of therapy will require long-term treatment and HBeAg negative chronic hepatitis B patients may need indefinite treatment, long-term safety was a critical consideration in selecting an effective and safe dose for registration. The selected dose had to have similar efficacy to 30 mg daily but without signs of nephrotoxicity. The efficacy and safety of the 10 mg daily dose of adefovir dipivoxil was confirmed by the results of the phase 3 clinical placebo-controlled studies as described in Sections 5.2 and 6.2, respectively.

Table 4. Results of Adefovir Dipivoxil Phase 1/Phase 2 Studies

Study	General Design	Patient Population	Patients Enrolled	Dose	Baseline Characteristics	Key Efficacy Results
GS-94-404	Double-Blind, Randomized, Placebo Controlled, Dose Escalation	HBeAg+ chronic hepatitis B	20	Initial: ADV 125 mg Maintenance: 60, 120 mg	*Age:* Median 35.9 yrs *Gender:* 100% male *HBV DNA:* Median 9.2 $\log_{10}$ pg/mL *ALT:* Median 97.5 IU/L	**Initial Phase:** Serum HBV DNA median change at week 4 (Digene Hybrid Capture Assay): ADV 125 mg: -3.99 $\log_{10}$ pg/mL (p=0.003) Placebo: 0.001 $\log_{10}$ pg/mL **Maintenance Phase:** Serum HBV DNA median change at week 24: ADV 60 mg: -3.26 $\log_{10}$ mEq/mL ADV 120 mg: -3.04 $\log_{10}$ mEq/mL (Chiron assay).
GS-96-412	Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Initial Phase	HBeAg+ and HBeAg- chronic hepatitis B, elevated ALT	53 10	ADV 5, 30, and 60 mg	*Age:* Median 36.0 yrs *Gender:* 74% male *HBV DNA:* Median 8.57 $\log_{10}$ copies/mL *ALT:* 99.0 IU/L	**Serum HBV DNA median change at week 12 (Roche Amplicor PCR assay) HBeAg + cohort:** ADV 5 mg: -1.82 $\log_{10}$ copies/mL ($p < 0.001$) ADV 30 mg: -3.78 $\log_{10}$ copies/mL ($p < 0.001$) ADV 60 mg: -3.34 $\log_{10}$ copies/mL ($p < 0.001$) Placebo: -0.02 $\log_{10}$ copies/mL **Seroconversion:** ADV 6/39 (15%); placebo 0/14 **HBeAg- cohort**: ADV 30 mg: -3.59 $\log_{10}$ copies/mL ($p = 0.037$) Placebo: -0.28 $\log_{10}$ copies/mL
GS-96-412 Ext.	Open-label	Continuation for patients completing studies 412 and 413	39	ADV 30 mg, reduced to 10 mg during study	*Age:* Median 41.0 yrs *Gender:* 85% male *HBV DNA:* Median 8.02 $\log_{10}$ copies/mL *ALT:* 83 IU/L	**Serum HBV DNA median change (Roche Amplicor PCR assay):** week 24: -3.68 $\log_{10}$ copies/mL ($p < 0.001$) week 48: -3.40 $\log_{10}$ copies/mL ($p < 0.001$) week 76: -3.33 $\log_{10}$ copies/mL ($p < 0.001$) **ALT normalization**: 19/30 (63%) at week 48, 20/26 (77%) at week 76, 19/22 (86%) at week 100. **Seroconversion:** ADV 6/28 (21%)
GS-96-413	Randomized, Double-Blind, Placebo-Controlled, Dose Escalation	HBV DNA+ chronic hepatitis B, normal ALT	14	ADV 30 mg	*Age:* Median 32.0 *Gender:* 60% male *HBV DNA:* Median 9.49 $\log_{10}$ copies/mL *ALT:* 34.0 IU/L	**Serum HBV DNA median change at week 12 (Roche Amplicor PCR assay)** ADV 30 mg: -2.83 $\log_{10}$ copies/mL ($p = 0.028$) Placebo: -0.03 $\log_{10}$ copies/mL

5.2. Phase 3 Placebo-Controlled Studies in Patients with Chronic Hepatitis B and Compensated Liver Disease: Studies 437 and 438

5.2.1. Study Design

Two randomized, double-blind, placebo-controlled studies, studies 437 and 438, investigated the efficacy and safety of adefovir dipivoxil 10 mg once daily in patients with chronic hepatitis B and compensated liver disease, who were not undergoing current treatment and had evidence of active liver disease. Study 437 also included a third treatment arm of adefovir dipivoxil 30 mg once daily. In study 437, HBeAg positive patients with chronic hepatitis B were enrolled while in study 438, the population was comprised of patients with HBeAg negative (presumed precore mutant) chronic hepatitis B. The primary endpoint for both studies was at week 48 for the comparison of adefovir dipivoxil 10 mg to placebo; both studies were designed with a 96 week treatment duration. Efficacy and safety data for 48 weeks of treatment are available for both studies. This treatment period is considered adequate to allow for histological changes in the liver to evolve and a sufficient period of time to establish the durability of the antiviral and clinical response.

Dosing Schedules

The dosing schedule for study 437 is summarized in Figure 1. In study 437 during the first 48 weeks of double-blind treatment, patients were randomized (1:1:1) and received one of three treatment regimens, adefovir dipivoxil 10 mg, adefovir dipivoxil 30 mg or placebo once daily. Because a metabolite of adefovir dipivoxil, pivalic acid conjugates with carnitine leading to a decrease in serum free carnitine levels, patients randomized to either adefovir dipivoxil 10 mg or placebo were further randomized to daily administration of either 250 mg of L-carnitine or L-carnitine placebo; all subjects within the adefovir dipivoxil 30 mg group received active L-carnitine. During the second 48 weeks of the study, patients who received adefovir dipivoxil 10 mg were re-randomized to receive adefovir dipivoxil 10 mg or placebo once daily; patients who received adefovir dipivoxil 30 mg received placebo for the second 48 weeks; and patients who received placebo received adefovir dipivoxil 10 mg.

Misallocation of Dosing in Study 437: Gilead Sciences became aware on July 12, 2001, that study medication had been misallocated by the Interactive Voice Response System during the second year of study 437 (on or after September 22, 2000). As a result, a total of 91% of patients who entered the second 48 week period received at least one incorrect bottle of study medication, i.e., patients due to receive adefovir dipivoxil received placebo and visa versa. Consequently, the ongoing blinded phase of the study was closed and patients were initially offered open-label adefovir dipivoxil 10 mg until further studies were opened, i.e., study 437 long-term efficacy and safety, study 480 (continued access) and study 481 (durability of seroconversion). Data collected during the first 48 weeks were unaffected by this error and analyses of the first 48 weeks were performed as planned in a blinded manner. Additional analyses were performed on the second 48 weeks of study 437, up until the first incorrect treatment assignment. Data were censored at the time the patient received the first incorrect treatment assignment.

Figure 1. Treatment Schedule in Study 437

Study Group	First Year of Study Dosing (0-48 Weeks)		Study Group	Second Year of Study Dosing (48-96 Weeks)
1	Adefovir dipivoxil 30 mg + L-carnitine 250 mg		1	Adefovir dipivoxil placebo
2a	Adefovir dipivoxil 10 mg + L-carnitine 250 mg	Re-randomize	2aα	Adefovir dipivoxil 10 mg
			2aβ	Adefovir dipivoxil placebo
2b	Adefovir dipivoxil 10 mg + L-carnitine placebo	Re-randomize	2bα	Adefovir dipivoxil 10 mg
			2bβ	Adefovir dipivoxil placebo
3a	Adefovir dipivoxil placebo + 250 mg L-carnitine		3a	Adefovir dipivoxil 10 mg
3b	Adefovir dipivoxil placebo + 250 mg L-carnitine placebo		3b	Adefovir dipivoxil 10 mg

The dosing schedule for study 438 is summarized in Figure 2. During the first 48 weeks of double-blind treatment, patients were randomized in a 2:1 ratio to receive either adefovir dipivoxil 10 mg or placebo once daily. During the second year, patients who received adefovir dipivoxil 10 mg were re-randomized at the end of the first 48 weeks, again in a 2:1 ratio, to receive adefovir dipivoxil 10 mg or placebo. Patients who received placebo in the first 48 weeks received adefovir dipivoxil 10 mg once daily for the second 48 weeks. Treatment assignments in year two remain blinded.

Figure 2. Treatment Schedule in Study 438

Study Group	First Year of Study Dosing (0-48 Weeks)	Study Group	Study Group	Second Year of Study Dosing (48-96 Weeks)
1	Adefovir dipivoxil 10 mg	Re-randomize	1a	Adefovir dipivoxil 10 mg
			1b	Adefovir dipivoxil placebo
2	Adefovir dipivoxil placebo		2	Adefovir dipivoxil 10 mg

Selection of Populations

The patients who participated in studies 437 and 438 form the two major groups of patients with chronic hepatitis B. Patients with HBeAg positive chronic hepatitis B (study 437) represent the majority of patients seen in North America and Europe. Patients with HBeAg negative (also referred to as presumed precore mutant) chronic hepatitis B (study 438) have been estimated to account for 7 to 30% of chronic infections worldwide.[30] This type of chronic hepatitis B exists worldwide and is generally due to the selection of an important variant form of HBV harboring a mutation in the precore region of the hepatitis B genome

that prevents the virus from producing HBeAg. Recent reports suggest that HBeAg negative chronic hepatitis B is more common than previously suspected; median prevalence of 33% in the Mediterranean, 15% in Asia Pacific and 14% in the United States and Northern Europe has been reported although more recent data indicates that the prevalence of HbeAg negative data is increasing in the US.[31] Compared with HBeAg positive disease, patients with HBeAg negative chronic hepatitis B have: (i) a more variable disease course characterized by large fluctuations over time in virus replication and disease activity with recurrent relapses which alternate with transient phases of remission, (ii) a lower rate of sustained spontaneous remission.

Principal entry criteria included evidence of active liver disease with viral replication and elevated ALT levels (≥ 1.2 times the upper limit of normal for study 437 and ≥ 1.5 times the upper limit of normal for study 438). Patients had to have compensated liver disease as well as adequate renal function (serum creatinine ≤ 1.5 mg/dL). Patients were also to be HIV, HCV, and HDV seronegative. Patients were not to be receiving any current therapy for chronic hepatitis B. Prior lamivudine or famciclovir therapy and interferon-α therapy was permitted provided the last dose was administered ≥ 6 months prior to the first screening visit (any prior nucleoside or nucleotide analogs with activity against HBV had to be limited to ≤ 12 weeks). Treatment with hepatotoxic drugs and nephrotoxic drugs or competitors of renal excretion was prohibited within 2 months prior to study screening and during the study.

Efficacy Endpoints and Statistical Method

The primary efficacy endpoint of studies 437 and 438 was based on the quantitative assessment of histological improvement at week 48 compared with baseline using the Knodell Histologic Activity Index (HAI) score.[32] Histological improvement was defined as a reduction from baseline of 2 points or more in the Knodell necroinflammatory score with no concurrent worsening in the Knodell fibrosis score. The primary analysis was performed in a subset of the intent-to-treat (ITT) population where an assessable baseline biopsy was available. Missing or unassessable 48 week biopsies were considered as treatment failure. The protocol originally specified a significance level $\alpha = 0.025$ for two pairwise comparisons between the adefovir dipivoxil dosage groups (10 and 30 mg) with placebo. On the basis of emerging data from study GS-96-412, the comparison between adefovir dipivoxil 10 mg was made the primary treatment comparison. This was to be conducted at a nominal two sided $\alpha = 0.05$ level of significance.

Assessment of pre-treatment and week 48 biopsies was performed in both studies at a single reading by the same histopathologist, who was blinded to both treatment assignment and biopsy sequence. A ranked histological assessment was also performed, where the histopathologist reviewed the two biopsies in a blinded fashion and assessed whether changes in necroinflammation and fibrosis between the baseline and week 48 biopsies were improved, remained the same, or worsened.

Secondary endpoints in the pivotal studies were based on established and well documented methods for determining the antiviral response (suppression of HBV replication as assessed

by the decrease of serum HBV DNA and the proportion of patients with HBV DNA < lower limit of quantification of the assay used) and biochemical response (as defined by reductions in ALT and rates of normalization) to therapy. HBeAg seroconversion, defined as loss of HBeAg and appearance of anti-HBe was also a key secondary endpoint in study 437. For the quantification of serum HBV DNA in the adefovir dipivoxil phase 3 studies, the most sensitive polymerase chain reaction (PCR) assay available at the time was utilized. This PCR assay (the Roche Amplicor™ PCR, nonradioactive hybridization assay, LLQ 400 copies/mL) is a reliable tool for the detection of HBV DNA in serum.[33]

As the two studies were of similar design, the analysis and reporting of data followed the same statistical analysis plan facilitating data comparisons between the studies. The primary comparison for both studies was between adefovir dipivoxil 10 mg and placebo.

5.2.2. Study Populations

The number of patients randomized to treatment in studies 437 and 438, the numbers who completed 48 weeks of treatment and reasons for discontinuation are summarized in Table 5. In both studies, nearly all patients completed the first 48 weeks of treatment.

The principal demographic and baseline characteristics of the populations in studies 437 and 438 are summarized in Table 6.

Data from studies 437 and 438, which enrolled primarily Caucasian and Asian patients, indicate that the response to treatment with adefovir dipivoxil 10 mg per day in Asian and Caucasian patients with chronic hepatitis B is likely to be similar. Relatively low numbers of Black patients were enrolled in the pivotal studies so racial comparisons could not be performed.

A higher proportion of Black patients were enrolled in study 472, an open-label, 7 day pharmacokinetic and pharmacodynamic study to be followed by 47 weeks of continued treatment with 10 mg daily of adefovir dipivoxil. Of the total of 14 evaluable patients with chronic hepatitis B, 5 were Caucasian (35.7%), 5 were Black (35.7%), and 4 were Asian (28.6%). No differences were observed in the pharmacokinetics of these patients. Overall in clinical studies with adefovir dipivoxil 10 mg, 8% of patients enrolled were Black.

Table 5. Disposition of Patients Up to 48 Weeks: Studies 437 and 438

	Study 437 HBeAg+				Study 438 HBeAg-		
Parameter	**Total**	**Placebo**	**ADV 10 mg**	**ADV 30 mg**	**Total**	**Placebo**	**ADV 10 mg**
Disposition	**n (%)**	**n (%)**	**n(%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of Patients Randomized	515	170	172	173	185	62	123
Received at Least One Dose (ITT)	511	167	171	173	184	61	123
Completed Treatment Up to 48 Weeks	472 (92%)	154 (92%)	159 (93%)	159 (92%)	180 (98%)	60 (98%)	120 (98%)
Discontinued Treatment Before Week 48	39 (8%)	13 (8%)	12 (7%)	14 (8%)	4 (2%)	1 (2%)	3 (2%)
Reasons for Discontinuation							
Adverse Event	10 (2%)	1 (< 1%)	4 (2%)	5 (3%)	1 (< 1%)	0 (0%)	1 (< 1%)
Withdrew Consent	13 (3%)	7 (4%)	3 (2%)	3 (2%)	2 (1%)	1 (2%)	1(< 1%)
Lost to Follow-up	4 (<1%)	1 (< 1%)	2 (1%)	1 (<1%)	1 (< 1%)	0 (0%)	1 (< 1%)
Disease Progression	2 (<1%)	1 (< 1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Patient Non-compliance	6 (1%)	2 (1%)	2 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Other	4 (<1%)	1 (< 1%)	1 (< 1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Assessable Biopsies							
No. of Patients at Baseline	511	167	171	173	184	61	123
No. w/Assessable Biopsies at Baseline	494 (97%)	161 (96%)	168 (98%)	165 (95%)	178 (97%)	57 (93%)	121 (98%)
No. w/Assessable Biopsies at Week 48	452 (88%)	150 (90%)	152 (89%)	150 (87%)	172 (93%)	58 (95%)	114 (93%)
No. w/Assessable Biopsies at Baseline and Week 48	441 (86%)	146 (87%)	150 (88%)	145 (84%)	167 (91%)	55 (90%)	112 (91%)

Note: The denominator for all percentages is the number of patients who received at least one dose of study medication.

Table 6. Demographic and Baseline Disease Characteristics: Studies 437 and 438

Characteristic	Study 437 (N = 511)	Study 438 (N = 184)
Population	***HBeAg+***	***Presumed Precore Mutant (HBeAg-)***
Age (years)		
Mean ± SD	35 ± 11.3	46 ± 10.0
Median	33	46
Q1, Q3	26, 43	39, 53
Gender		
Male, n (%)	378 (74%)	152 (83%)
Female, n (%)	133 (26%)	32 (17%)
Race		
Caucasian, n (%)	184 (36%)	122 (66%)
Black, n (%)	16 (3%)	6 (3%)
Asian, n (%)	304 (59%)	56 (30%)
Other, n (%)	7 (1%)	0 (0%)
Knodell HAI Scores		
Total		
Mean ± SD	9.40 ± 3.37	9.38 ± 3.33
Median	10	10
Q1, Q3	8, 12	8, 12
Necroinflammatory		
Mean ± SD	7.67 ± 2.82	7.52 ± 2.74
Median	8	7
Q1, Q3	7, 10	5, 10
Fibrosis		
Mean ± SD	1.72 ± 1.09	1.86 ± 1.16
Median	1	1
Q1, Q3	1, 3	1, 3
Cirrhosis	32 (6%)	20 (11%)
HBV DNA (log_{10} copies/mL)		
Mean ± SD	8.20 ± 0.88	6.93 ± 0.89
Median	8.36	7.08
Q1, Q3	7.61, 8.82	6.33, 7.55
ALT (IU/L)		
Mean ± SD	133.77 ± 129.00	145.59 ± 151.54
Median	94	98
Q1, Q3	65, 158	69, 165
> ULN	501 (98%)	175 (95%)
Prior HBV Meds		
Interferon-α	123 (24%)	76 (41%)
Lamivudine	10 (2%)	14 (8%)

5.2.3. Efficacy Results

In the following section, the primary focus is on the efficacy results for the adefovir dipivoxil 10 mg and placebo groups in studies 437 and 438 since this was the primary comparison in both studies. An overview of the efficacy results for the 30 mg dose in study 437 is also included with more detailed results for all three treatments arms in this study (placebo, adefovir dipivoxil 10 mg and adefovir dipivoxil 30 mg) provided in Appendix 3.

5.2.3.1. Efficacy of Adefovir Dipivoxil 10 mg Daily

Results for Primary Efficacy Endpoint:

In both studies 437 and 438, treatment with adefovir dipivoxil 10 mg daily demonstrated statistically significant improvements in liver histology from baseline after 48 weeks of treatment compared with placebo (improvement defined as a reduction from baseline of 2 points or more in the Knodell necroinflammatory score with no concurrent worsening of the Knodell fibrosis score). The differences in the proportion of patients with improvement between the placebo group and adefovir dipivoxil 10 mg group after 48 weeks of treatment were similar in the two studies: 28% of the HBeAg positive patients in study 437 and 30% of the HBeAg negative patients in study 438 (Table 7).

Table 7. Results of Primary Efficacy Parameter - Histological Improvement at Week 48: Studies 437 and 438

	Study 437 HBeAg+		Study 438 HBeAg-	
ITT (Missing/Unassessable Week 48 Biopsies = Failure)	**Placebo (N = 167)**	**ADV 10 mg (N = 171)**	**Placebo (N = 61)**	**ADV 10 mg (N = 123)**
n (with baseline biopsy)	161	168	57	121
Improvement[1], n (%)	41 (25%)	89 (53%)	19 (33%)	77 (64%)
No improvement, n (%)	105 (65%)	61 (36%)	36 (63%)	35 (29%)
Missing/unassessable, n (%)	15 (9%)	18 (11%)	2 (4%)	9 (7%)
Treatment difference[2], % (95% CI)	27.5% (17.4%, 37.6%)		30.3% (15.4%, 45.2%)	
p-value[3]	< 0.001		< 0.001	

1 Improvement defined as ≥ 2 point decrease in Knodell necroinflammatory score from baseline at Week 48 with no concurrent worsening in the Knodell fibrosis score. Missing postbaseline biopsies were considered failures.

2 Treatment difference (95% confidence interval) for proportion of patients with improvement.

3 From general association Cochran-Mantel-Haenszel statistic unstratified.

Results for Secondary Efficacy Endpoints:

The results of secondary efficacy endpoints for studies 437 and 438 are summarized in Table 8.

Table 8. Overview of Results of Secondary Efficacy Parameters: Studies 437 and 438

Efficacy Variable at Week 48	Study 437 HBeAg+			Study 438 HBeAg-		
	Placebo (N = 167)	ADV 10 mg (N = 171)	p-value	Placebo (N = 61)	ADV 10 mg (N = 123)	p-value
Liver Histology (Knodell Scores), ITT[1]						
Mean ± SD Change from Baseline:						
- Total Score	-0.17 ± 3.51	-2.76 ± 3.60	< 0.001	0.44 ± 3.68	-3.72 ± 3.13	< 0.001
- Necroinflammatory Score	-0.16 ± 3.06	-2.58 ± 3.22	< 0.001	0.31 ± 3.21	-3.43 ± 2.87	< 0.001
- Fibrosis Score	-0.01 ± 0.86	-0.18 ± 0.84	0.061	0.13 ± 0.94	-0.29 ± 0.74	< 0.005
HBV DNA						
Serum HBV DNA < 400 copies/mL, %	0%	21%	< 0.001	0%	51%	< 0.001
Median Change (log_{10} copies/mL)	-0.55	-3.52	< 0.001	-1.35	-3.91	< 0.001
DAVG (log_{10} copies/mL)[2]	-0.43	-2.84	< 0.001	-0.87	-3.53	< 0.001
ALT						
Normalized, %	16%	48%	< 0.001	29%	72%	< 0.001
Median Change (IU/L)	-17	-51	< 0.001	-38	-55	< 0.001
Serology						
% of Patients with HBeAg Seroconversion[3]	6%	12%	< 0.05			
% of Patients with HBeAg Loss	11%	24%	< 0.01			

1 Results of blinded ranked assessment are presented in Figure 3 (study 437) and Figure 4 (study 438).

2 Time-weighted average change from baseline.

3 Defined as loss of HBeAg and appearance of anti-HBe

Secondary efficacy endpoints demonstrate statistically significant benefits across a range of clinical, virological and laboratory endpoints in patients treated with adefovir dipivoxil 10 mg once daily for 48 weeks.

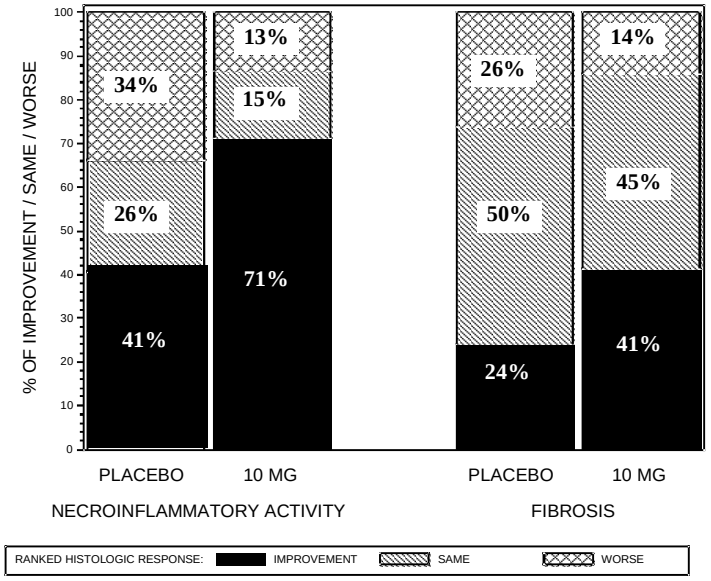
With respect to liver histology, statistically significant changes from baseline in the total Knodell HAI score, the necroinflammatory portion of the Knodell score, and the fibrosis portion of the Knodell score (study 438 only) were demonstrated for adefovir dipivoxil 10 mg groups compared with placebo. Results of the ranked histological assessment are presented for study 437 in Figure 3 and for study 438 in Figure 4. On ranked assessment, both necroinflammatory activity and fibrosis showed greater improvement in patients treated with adefovir dipivoxil 10 mg compared with placebo recipients ($p < 0.001$). Worsening of necroinflammatory activity and fibrosis was seen in a greater proportion of the placebo groups.

In addition to improvements in liver histology, the antiviral efficacy of adefovir dipivoxil 10 mg was demonstrated with respect to statistically significant reductions in serum HBV DNA levels as determined by median changes from baseline, $DAVG_{48}$ and proportion with undetectable HBV DNA (Roche Amplicor™ PCR assay, LLQ < 400 copies/mL). As shown in Figure 5 and Figure 6, median serum HBV DNA levels fell rapidly in the adefovir dipivoxil 10 mg group over the first 4 weeks of treatment and then continued to decrease at a consistent rate over the course of the study. There was a higher proportion of HBeAg negative patients with serum HBV DNA < 400 copies/mL at week 48 in study 438 compared with the HBeAg positive patients of study 437; patients in study 438 had lower baseline serum HBV DNA levels than in study 437.

In addition to the direct antiviral benefit, patients treated with adefovir dipivoxil 10 mg had statistically significant reductions in serum ALT levels, and a higher proportion achieved ALT normalization compared with placebo patients. The median changes in ALT during 48 weeks of treatment are displayed in Figure 7 for study 437 and Figure 8 for study 438. Although study 438 showed a higher proportion of patients achieving ALT normalization compared with study 437, the magnitude of the reduction in both studies was similar, indicating a similar response to treatment. The increased number of patients with ALT normalization in study 438 may reflect the difference in severity of disease at baseline in the two studies.

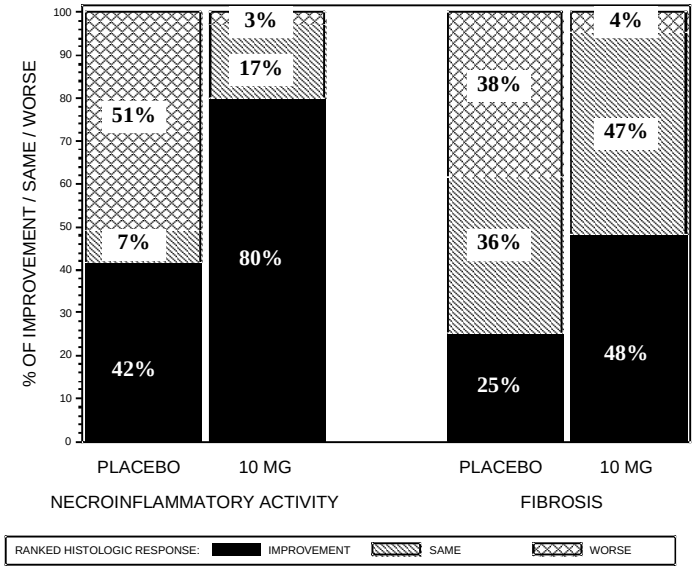
In patients with HBeAg positive chronic hepatitis B (study 437), a significantly greater proportion of patients on active treatment achieved HBeAg loss and HBeAg seroconversion (loss of HBeAg and development of anti-HBe). HBeAg loss and HBeAg seroconversion were associated with ALT normalization and HBV DNA suppression in the majority of patients in the active treatment group compared with few patients in the placebo group.

Figure 3. Results of Ranked Necroinflammatory and Fibrosis Histological Assessments: Study 437 (HBeAg+ Patients) at Week 48



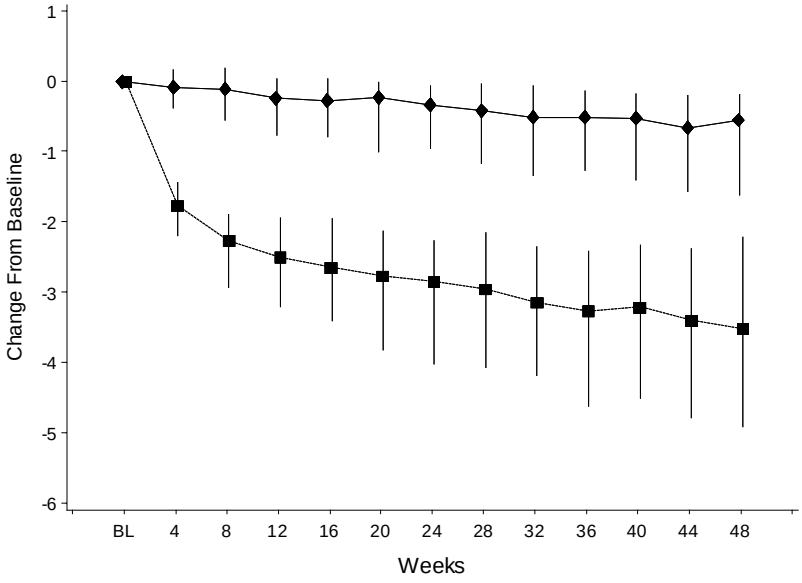
Each pair of specimens was assessed to determine whether one specimen showed more severe necroinflammatory activity or more fibrosis than the other (ranked response).

Figure 4. Results of Ranked Necroinflammatory and Fibrosis Histological Assessments: Study 438 (HBeAg- Patients) at Week 48



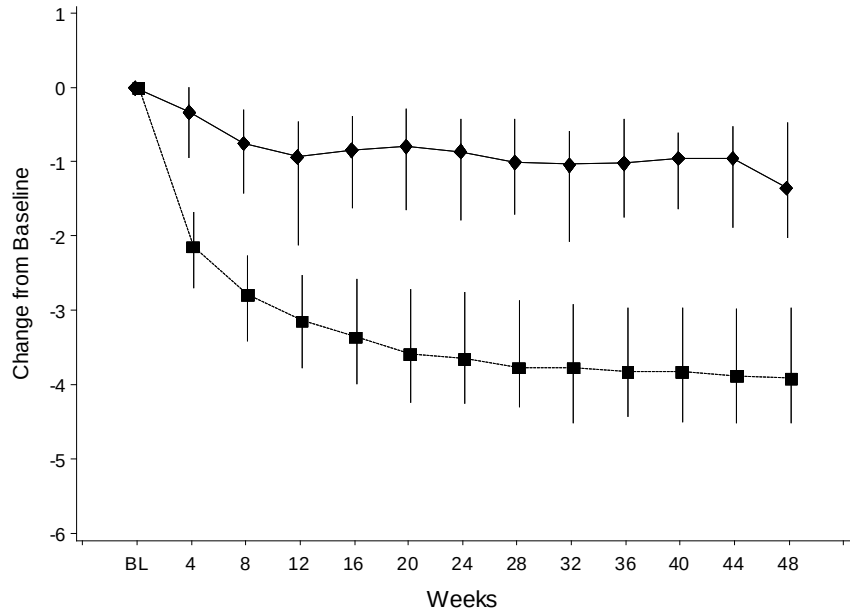
Each pair of specimens was assessed to determine whether one specimen showed more severe necroinflammatory activity or more fibrosis than the other (ranked response).

Figure 5. Median and Interquartile Range of Change in HBV DNA (Log_{10} Copies/mL) from Baseline (ITT): Study 437 HBeAg+



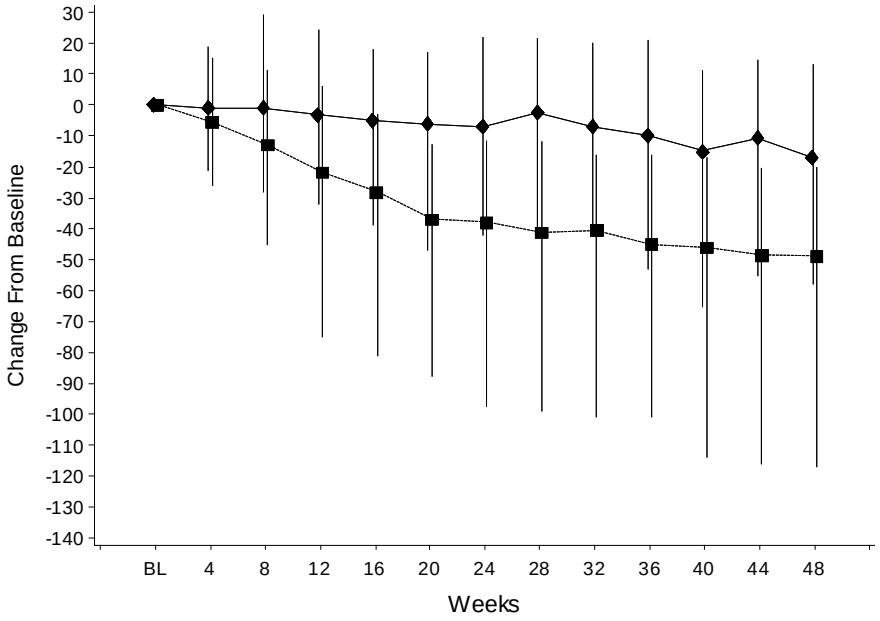
◆ PLACEBO (N=):	167	164	162	162	158	158	156	156	153	153	152	150	148
■ 10 MG (N=):	171	164	170	168	164	164	160	165	156	150	157	157	152

Figure 6. Median and Interquartile Range of Change in HBV DNA (Log_{10} Copies/mL) from Baseline (ITT): Study 438 HBeAg-



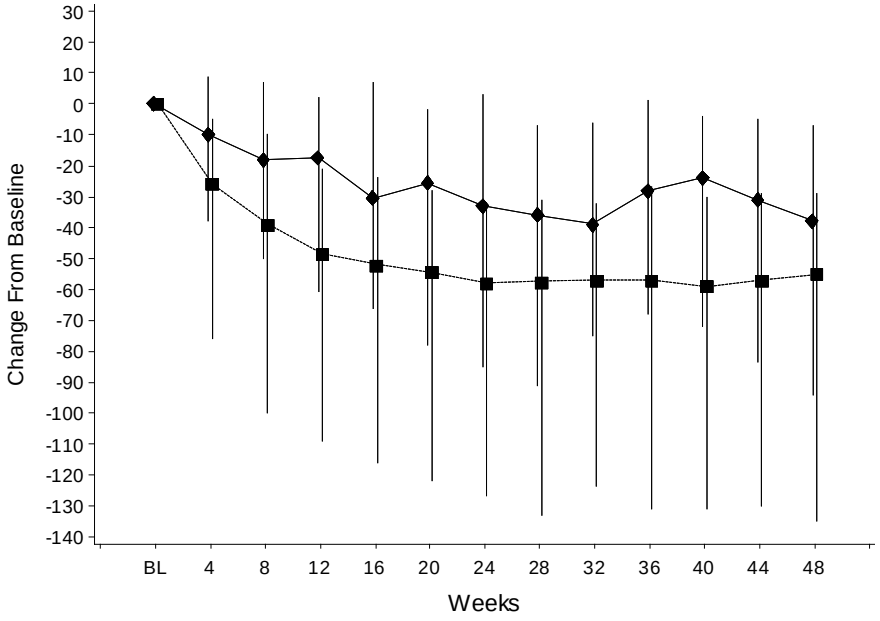
◆ PLACEBO (N=):	61	61	57	58	58	58	56	58	59	57	59	60	55
■ 10 MG (N=):	123	120	116	115	122	117	116	121	119	119	121	122	117

Figure 7. Median and Interquartile Range of Change in ALT (IU/L) from Baseline (ITT): Study 437 HBeAg+



◆ PLACEBO (N=):	167	165	163	163	161	157	157	152	151	153	149	148	147
■ 10 MG (N=):	171	166	170	166	162	163	156	163	158	150	156	156	150

Figure 8. Median and Interquartile Range of Change in ALT (IU/L) from Baseline (ITT): Study 438 HBeAg-



◆ PLACEBO (N=):	61	61	61	56	58	60	57	55	59	59	59	60	55
■ 10 MG (N=):	123	121	119	118	123	118	117	114	120	117	119	121	118

5.2.3.2. Efficacy of Adefovir Dipivoxil 30 mg Daily

A comparison of the results of the adefovir dipivoxil 10 mg and 30 mg treatment groups in study 437 for the primary and key secondary efficacy parameters is presented in Table 9. More detailed results are provided in Appendix 3. Treatment with adefovir dipivoxil 30 mg resulted in similar histological, serological and ALT responses to those observed with adefovir dipivoxil 10 mg. For some endpoints, for example, reduction in serum HBV DNA levels, the response to the higher dose appeared numerically higher, although statistical comparisons between these groups were not performed. However, as described in Section 5.1, the 30 mg dose of adefovir dipivoxil is not considered the optimal therapeutic dose for treatment of chronic hepatitis B because of the emergence of mild nephrotoxicity with long-term dosing.

Table 9. Overview of Efficacy Results By Dose Group: Study 437

Efficacy Variable at Week 48	Placebo (N = 167)	ADV 10 mg (N = 171)	ADV 30 mg (N = 173)
Liver Histology (Knodell HAI Scores)			
Primary Endpoint			
Histological Improvement[1], n/N (%)	41/161 (25%)	89/168 (53%)	98/165 (59%)
p-value		< 0.001	< 0.001
Total Knodell HAI			
Mean ± SD Change from Baseline	-0.17 ± 3.51	-2.76 ± 3.60	-3.48 ± 3.66
p-value		< 0.001	< 0.001
Serum HBV DNA			
< 400 copies/mL, n (%)	0 (0%)	36 (21%)	67 (39%)
p-value		< 0.001	< 0.001
Median DAVG $_{48}$ ($\log_{10}$ copies/mL)[2]	-0.43	-2.84	-4.10
p-value		< 0.001	< 0.001
ALT Levels			
Normalized, n/N (%)	26/164 (16%)	81/168 (48%)	93/169 (55%)
p value		< 0.001	< 0.001
Serology			
HBeAg loss, n (%)	17 (11%)	41 (24%)	44 (27%)
p value		< 0.01	< 0.001
HBeAg seroconversion[3], n (%)	9 (6%)	20 (12%)	23 (14%)
p value		< 0.05	< 0.011

1 Improvement defined as ≥ 2 point decrease in Knodell necroinflammatory score from baseline at week 48 with no concurrent worsening in the Knodell fibrosis score.

2 Time-weighted average change from baseline.

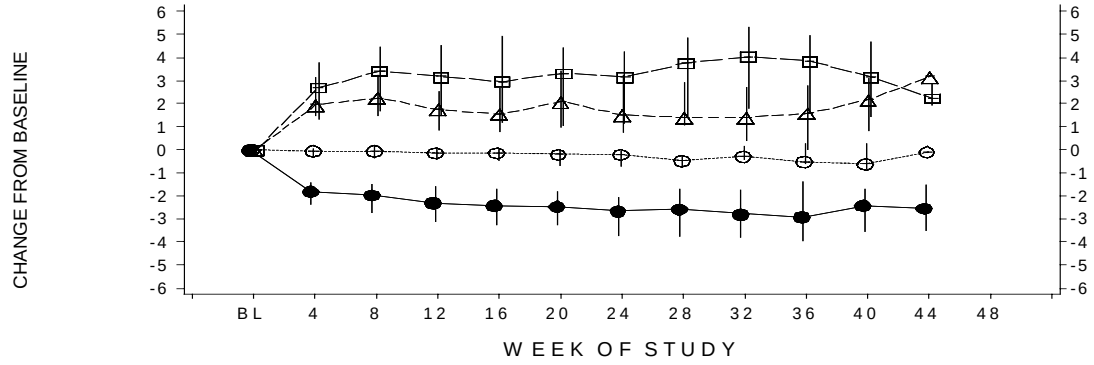
3 Defined as loss of HBeAg and appearance of anti-HBe.

5.2.3.3. Durability of Treatment Response Past 48 Weeks

Studies 437 and 438 are both ongoing with patients re-randomized at the end of the first 48 weeks of treatment according to the treatment schedules illustrated in Figure 1 and Figure 2. Interim efficacy results were presented for the second 48-week treatment period in the NDA.

Efficacy analyses of the second 48 weeks in study 437 were performed on data up until the first incorrect treatment assignment, at which point the data were censored. Eighty-five patients treated with adefovir dipivoxil 10 mg during the first 48 weeks continued to receive adefovir dipivoxil 10 mg during the second 48 weeks (median duration of treatment in the second 48 weeks was 15.6 weeks). There was a continued decline in serum HBV DNA from the year 2 baseline value (median 5.17 $\log_{10}$ copies/mL) during the second 48 weeks of study 437 among patients who remained on adefovir dipivoxil 10 mg, with a median additional reduction from the second 48 week baseline of -0.13 $\log_{10}$ copies/mL at week 12 (n = 54) and -0.21 $\log_{10}$ copies/mL at week 24 (n = 29). Changes in serum HBV DNA for all treatment groups in the second 48 weeks of study 437 are displayed graphically in Figure 9.

Figure 9. Median and Interquartile Range of Change in HBV DNA (Log_{10} Copies/mL) from Baseline During Second 48 Weeks of Treatment of Study 437 HBeAg+

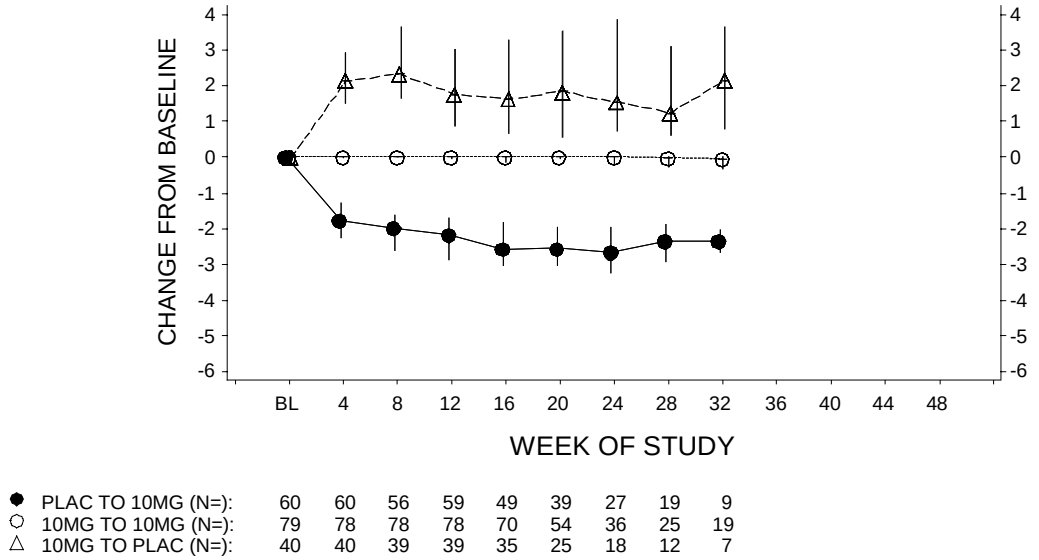


Among patients who had serum HBV DNA levels > 400 copies/mL at the beginning of the second 48 weeks in study 437, 15 of 71 patients (21%) who remained on adefovir dipivoxil 10 mg had serum HBV DNA levels < 400 copies/mL at their last evaluation. Continued improvement of ALT levels was also demonstrated. Of the 85 patients who remained on adefovir dipivoxil 10 mg, 41 had ALT values > ULN at the 48 week baseline. At the time of the analysis, 11 of the 41 patients (27%) had normal ALT values. Among patients who did

not undergo HBeAg seroconversion during the first 48 weeks of study 437, 4 of 74 patients (5%) who remained on adefovir dipivoxil 10 mg underwent HBeAg seroconversion (loss of HBeAg and development of anti-HBe) and 10 of 62 patients (16%) experienced HBeAg loss at the time of the analysis.

The interim results for the second 48 week treatment period in study 438 also demonstrate additional antiviral benefit for patients who continued to receive adefovir dipivoxil 10 mg. In this group, 36 of 79 patients had serum HBV DNA levels ≥ 400 copies mL at the start of the second 48 week treatment period. At the time of reporting, 16/36 (44%) had serum HBV DNA levels below 400 copies/mL at their last evaluation. Changes in serum HBV DNA from baseline are displayed graphically in Figure 10. Nineteen of the 79 patients (24%) who remained on adefovir dipivoxil 10 mg had ALT values > ULN at the second 48 week baseline, and 4 had normal ALT values by the time of this interim analysis. One patient who remained on adefovir dipivoxil 10 mg experienced HBsAg seroconversion during year 2 at week 72, defined as a loss of HBsAg with concurrent gain of HBsAb. By week 28, the patient's serum HBV DNA was below 400 copies/mL and ALT levels were normal and they remained so throughout all subsequent evaluations.

Figure 10. Median and Interquartile Range of Change in HBV DNA (Log_{10} Copies/mL) from Baseline During Second 48 Weeks of Study 438 HBeAg-



5.2.4. Results of Subgroup Analyses

Treatment with adefovir dipivoxil 10 mg in patients with HBeAg positive and HBeAg negative chronic hepatitis B resulted in histological improvement compared with placebo in all subgroups investigated. A treatment effect (i.e., difference between adefovir dipivoxil 10 mg and placebo groups in the proportion of patients with histological improvement) was demonstrated regardless of demographic characteristics (age, gender, race), prior interferon-α therapy, and baseline hepatitis B disease status (assessed as baseline total Knodell HAI score, baseline serum HBV DNA levels, and baseline ALT levels).

In conclusion, the subgroup analyses for studies 437 and 438 demonstrate that the histological improvement associated with adefovir dipivoxil 10 mg is likely to be similar regardless of demographic or baseline disease status.

5.2.5. Results of Genotypic and Phenotypic Analyses

HIV_{IIIB} variants with reduced susceptibility to adefovir have been selected *in vitro*.[34, 35] Viruses with 12- to 15-fold reduced susceptibility to adefovir were obtained after > 30 passages. These viruses carried a K65R substitution in RT and were also cross-resistant to zalcitabine, didanosine, and lamivudine.[34] In another *in vitro* selection, viruses that carried a K70E substitution in RT emerged.[35] Although HIV RT and HBV polymerase have some degree of sequence homology, codons 65 and 70 are in a region of HIV RT that is not highly conserved within the HBV DNA polymerase. There was therefore no specific mutation on which to focus phenotypic and genotypic analyses.

Of particular importance to the assessment of efficacy are the results of the virology substudies of studies 437 and 438. As prospectively defined, the pol/RT domain of the HBV DNA polymerase gene from serum samples (with HBV DNA ≥ 400 copies/mL) from all patients was sequenced at baseline, at week 48, or upon early termination. *In vitro* phenotypic analyses of adefovir susceptibility were performed for all emerging amino acid substitutions at conserved residues of HBV DNA polymerase. All genotypic and phenotypic analyses were performed in a treatment-blinded fashion.

In the virology substudies of studies 437 and 438, no HBV mutations associated with resistance to adefovir were identified in either HBeAg positive or HBeAg negative chronic hepatitis B patients with up to 48 weeks of treatment with adefovir dipivoxil. A summary of the findings of each study is provided below.

(Note that a summary of the *in vitro* evaluation of the antiviral activity of adefovir dipivoxil is provided in Appendix 1.).

Virology Results of Study 437:

In study 437, paired baseline and week 48 sequences were obtained for 381 of 511 patients (166, 131, and 84 in the placebo, 10 mg, and 30 mg arms, respectively). The remaining patient samples were not genotyped, mostly because of undetectable serum HBV DNA levels (< 400 copies/mL) at week 48 in adefovir dipivoxil-treated patients.

A similar percentage of HBV isolates with amino acid substitutions in the pol/RT domain of HBV polymerase were isolated from patients in the placebo arm (34/166, 20%) and in the adefovir dipivoxil arms (47/215, 22%). The majority of substitutions occurred at polymorphic sites (135/145, 93%). No substitution occurred exclusively in the adefovir dipivoxil-treated arms and no mutation occurred at a frequency of > 1.6%. The polymorphic substitutions did not correlate with a reduction in HBV DNA suppression or a reduction in liver histology improvement in adefovir dipivoxil-treated patients.

Seven different novel substitutions occurred at conserved sites in the HBV polymerase in seven patients. Four of the seven patients were in one of the adefovir dipivoxil arms and three were in the placebo arm. *In vitro* phenotypic analyses showed that all four substitutions observed in the adefovir arms remained fully susceptible to adefovir. Furthermore, emergence of these substitutions was not associated with a loss of HBV DNA suppression (Table 10).

Table 10. *In Vitro* Phenotypic Analyses Results and HBV DNA Responses in Adefovir Dipivoxil-Treated Patients with Emerging Conserved Site Substitutions in Study 437

Patient ID	Amino Acid Substitution at Week 48	Treatment Arm	IC_{50} Fold Change[1]	Δ in HBV DNA at Week 48 (Log_{10} copies/mL)	HBV DNA Rebound[2]
0329-1072	S467A	10 mg	0.6	-4.1	No
0456-7006	H481L	30 mg	1.8[3]	-3.3	No
0517-7019	V562A	30 mg	1.1	-4.4	No
0510-4001	H582Q	10 mg	3.6	-5.9	No

1 Ratio of IC_{50} (mutant)/IC_{50} (wild-type) in cell culture assay. An adefovir resistance phenotype is defined as a ≥ 10-fold increase in IC_{50} for a mutant HBV compared with wild-type HBV.

2 HBV DNA rebound is pre-defined as a 1.0 log_{10} or greater increase in serum HBV DNA from nadir to the last HBV DNA measurement up to 48 weeks.

3 Ratio of K_i (mutant)/ K_i (wild-type) in enzymatic assay because the H481L mutant HBV strain was replication defective in cell culture. An adefovir resistance phenotype is defined as a ≥ 5-fold increase in K_i of adefovir diphosphate for a mutant HBV polymerase compared with wild-type HBV polymerase.

Using a predefined virological rebound definition of a single 1.0 log_{10} copies/mL increase or greater from nadir to the last HBV DNA measurement up to 48 weeks, 44 (27%) placebo patients and 26 (12%) adefovir dipivoxil-treated patients were identified as rebounders. The observation of a higher percentage of rebounders in the placebo arm than in the adefovir dipivoxil arms suggests that HBV DNA rebound, according to this definition, is largely attributable to natural fluctuation of HBV DNA levels. Four of the 26 adefovir dipivoxil 10 mg patients had emerging substitutions in the HBV polymerase; all substitutions were polymorphic variants that were also observed to be present in the baseline HBV isolates of other patients at baseline in whom there was no evidence of an effect of the substitution on HBV DNA suppression by adefovir dipivoxil. Thus, the observed HBV DNA rebound in the 4 adefovir dipivoxil treated patients with emerging substitutions and the 22 patients without

substitutions appears to be due to either drug compliance issues or natural fluctuation of HBV DNA levels.

Virology Results of Study 438:

Paired baseline and week 48 sequences of the pol/RT domain of the HBV polymerase gene were obtained for 117 of 184 patients (56 in the adefovir dipivoxil arm and 61 in the placebo arm). Sixty-seven patients treated with adefovir dipivoxil (54%) were not genotyped as these patients had serum HBV DNA levels < 400 copies/mL at week 48.

More patients in the placebo arm (29/61, 48%) than in the adefovir dipivoxil arm (18/56, 32%) developed amino acid substitutions in the pol/RT domain of HBV polymerase. Most substitutions occurred at polymorphic sites (113/122, 93%); no mutations occurred at a frequency of > 2.6% (3/117). Four different novel substitutions occurred at conserved sites in the HBV polymerase in three patients. All three patients were in the placebo arm. *In vitro* phenotypic analyses showed that all four mutations remained fully susceptible to adefovir.

Using the virological rebound definition of a single 1.0 $\log_{10}$ increase or greater from nadir to the last HBV DNA measurement up to 48 week, 19 (31%) placebo patients and 5 (9%) adefovir dipivoxil treated patients were identified as rebounders. Of the 5 rebounders in the adefovir dipivoxil arm, three did not develop any substitutions in HBV polymerase and two developed a total of 14 substitutions. All 14 substitutions were polymorphic variants present in other patient HBV isolates at baseline. Analysis of the responses of patients with the substitutions present at baseline revealed none of these 14 substitutions individually influenced HBV DNA suppression by adefovir dipivoxil.

5.3. Supportive Studies of Adefovir Dipivoxil in Patients with Chronic Hepatitis B Failing Lamivudine Therapy

The NDA reported interim results from four supportive clinical studies (see Table 3 in Section 4) conducted in patients with chronic hepatitis B who were receiving long-term lamivudine therapy and had diminished therapeutic response as evidenced by increasing ALT and serum HBV DNA levels. A summary of the principal efficacy results of each of these studies is presented below. These studies confirmed the antiviral efficacy of adefovir dipivoxil 10 mg once daily in terms of its ability to significantly reduce serum HBV DNA levels in the presence of lamivudine resistant HBV.

Study 435, (n = 324 in safety update) is an open-label study in liver transplantation patients (both pre- and post-transplantation) with lamivudine-resistant HBV, which was conducted to evaluate the efficacy and safety of adefovir dipivoxil in this population of medically compromised patients. Efficacy data for the post-transplantation cohort (A) were available for reporting in the NDA. This population included both HBeAg positive and HBeAg negative patients, and patients with either compensated and decompensated liver disease including patients with significant medical comorbidities. Adefovir dipivoxil 10 mg resulted in rapid and statistically significant reductions in serum HBV DNA levels (as assessed by $DAVG_{24}$ and $DAVG_{48}$ and median changes from baseline) that were durable through 48 weeks. The antiviral response was consistent regardless of the baseline pattern of lamivudine-resistant HBV mutations.

Improvements were also demonstrated with respect to other secondary clinical and biochemical endpoints (e.g., ALT and AST). Clinical response was confirmed by the statistically significant reduction from baseline in Child-Pugh-Turcotte score (ascites, encephalopathy, albumin, bilirubin, prothrombin time).

Post-NDA, an updated evaluation provided efficacy results to support the risk-benefit assessment for patients participating in study 435 (submitted to FDA June 2002). Efficacy data for 196 cohort A (patients post-liver transplantation) and 128 cohort B (patients waitlisted for liver transplantation) patients, with median durations of treatment of 56.1 and 18.7 weeks, respectively, were included in this evaluation. The results of the updated analyses demonstrate similar antiviral and clinical benefits of treatment with adefovir dipivoxil 10 mg in patients waitlisted for transplantation (cohort B) or post-liver transplantation (cohort A). Further results from this study are provided in Appendix 4.

In study 461, (n = 59) a randomized, active-controlled multicenter study in patients with compensated liver disease and lamivudine-resistant HBV, treatment with adefovir dipivoxil 10 mg resulted in a significant decrease in serum HBV DNA levels after 16 weeks of treatment (primary endpoint) compared with lamivudine monotherapy. Similar antiviral efficacy was demonstrated regardless of whether adefovir dipivoxil was dosed with or without lamivudine 100 mg ($p < 0.001$). No discernable antiviral effect was seen in patients continuing on lamivudine 100 mg monotherapy. A significantly greater proportion of patients had normalized ALT levels by week 16 in the adefovir dipivoxil 10 mg and combined adefovir dipivoxil/lamivudine groups compared with lamivudine monotherapy ($p < 0.05$). One patient in the adefovir dipivoxil 10 mg group seroconverted to anti-HBe at week 4, which was sustained at week 16. This study remains ongoing and patients have been followed out to 48 weeks. Forty-eight week data are now available from this study.

In an open-label, investigator-initiated, single center study in patients co-infected with HIV (study 460i), the efficacy of adefovir dipivoxil 10 mg when added to continuing lamivudine was demonstrated with statistically significant reductions in serum HBV DNA levels compared to baseline throughout the course of treatment up to 48 weeks ($p < 0.001$). [36] Thirty-five percent of patients had achieved ALT normalization by week 48. Of the 33 HBeAg positive patients at baseline, 4 (12%) became HBeAg negative, 3 of whom also became anti-HBe positive (3/33, 10%). In this study, no amino acid substitutions potentially associated with resistance to adefovir developed in the HBV polymerase of 20 genotyped patients who received adefovir dipivoxil 10 mg daily for 48 weeks were identified. Fifteen patients were unable to be genotyped as HBV DNA levels were suppressed to very low levels. In addition, 48 weeks of adefovir dipivoxil 10 mg daily dosing did not lead to the emergence of the adefovir resistance mutations K65R or K70E in the HIV reverse transcriptase of 13 genotyped patients. Patients continued to receive treatment in this study and at weeks 72 and 96 continued reductions in serum HBV DNA levels were seen compared to baseline. Ninety-six week data are now available.

In study 465, an ongoing, multicenter trial, sponsored by GlaxoSmithKline, where adefovir dipivoxil 10 mg open-label was added to ongoing lamivudine 100 mg was effective for the treatment of lamivudine-resistant chronic hepatitis B in patients with compensated liver

disease (Stratum B). At week 24, all patients achieved an HBV DNA response (defined as an absolute serum HBV DNA concentration ≤ 5 $\log_{10}$ copies/mL or a ≥ 2 $\log_{10}$ copies/mL reduction from baseline by Roche COBAS Amplicor HBV Monitor™ assay). Fifteen percent (6/39) of patients achieved undetectable HBV DNA (< 200 copies/mL). Three of 29 patients (10%) who were HBeAg positive at baseline became HBeAg negative at week 24. Clinical benefit was demonstrated by significant normalization in ALT, improvement in markers of hepatic function (bilirubin, albumin, pro-thrombin time) and improvement in Child-Pugh-Turcotte score. This study also had an additional controlled arm (Stratum A) where adefovir dipivoxil 10 mg added to ongoing lamivudine 100 mg was compared to continued lamivudine 100 mg alone in patients with compensated liver disease. This study was of 52 weeks duration. Fifty-two week data are now available for this cohort.

As summarized in Table 11, the antiviral and clinical efficacy of adefovir dipivoxil demonstrated in lamivudine-resistant patients (study 435 and the 3 supportive studies) was of a similar magnitude to that demonstrated in the placebo-controlled phase 3 studies in patients with HBeAg positive and HBeAg negative chronic hepatitis B and compensated liver disease.

5.4. Conclusions of Efficacy Assessment

In patients with chronic hepatitis B and compensated liver disease, treatment with adefovir dipivoxil 10 mg once daily, demonstrated statistically significant effects compared with placebo with respect to histological improvement (the primary endpoint), and for all secondary endpoints investigated including the proportion of patients with HBeAg seroconversion, reduction in serum HBV DNA levels (changes from baseline and proportion with undetectable HBV DNA by Roche Amplicor PCR, LLQ < 400 copies/mL) and ALT levels (changes from baseline and proportion of patients with ALT normalization) when compared with placebo. The effectiveness of adefovir dipivoxil was consistent across both HBeAg positive and HBeAg negative chronic hepatitis B patients.

There was no evidence of development of adefovir-associated resistance mutations in the HBV DNA polymerase during 48 weeks of treatment in the placebo-controlled phase 3 studies or in patients treated up to 136 weeks in the phase 2 program extension study. The absence of resistance to date is a key distinguishing feature of adefovir dipivoxil therapy compared with lamivudine therapy suggesting that adefovir dipivoxil 10 mg may have a high threshold to the development of resistance.

The significant effects of adefovir dipivoxil 10 mg are maintained in populations of patients with chronic hepatitis B who are failing current lamivudine therapy due to the development of YMDD mutants. Consistent antiviral and clinical efficacy has been demonstrated in lamivudine-resistant patients including post-liver transplantation patients, patients waitlisted for transplantation, patients with compensated and decompensated liver disease and patients co-infected with HIV. The antiviral response in post-liver transplantation patients was consistent regardless of the pattern of lamivudine resistant mutations present at baseline.

Table 11. Reductions in Serum HBV DNA and ALT Levels by Study for Principal and Supportive Studies

Study Number	Population with Chronic Hepatitis B (N=ADV 10 mg, ITT)	Median HBV DNA (log_{10} copies/mL)			Median ALT Reduction (IU/L)		
		Baseline	Change at Week 24	Change at Week 48	Baseline	Change at Week 24	Change at Week 48
Pivotal Studies							
Study 437	HBeAg positive/ compensated liver disease (n=171)	8.40	-2.85	-3.52	95	-38	-51
Study 438	HBeAg negative/ compensated liver disease (n=123)	7.10	-3.65	-3.91	93	-39	-55
Supportive Studies in Lamivudine-Resistant Populations							
Study 435	Post-liver transplantation/ lamivudine-resistant HBV (n=169)[a]	A: 8.2	A: -3.6	A: -4.3	A: 83	A: -29	A: -30
	Waitlisted for transplantation/ lamivudine-resistant HBV (n=103)[a]	B: 7.4	B: -3.7	B: -4.1	B: 75	B: -27.5	B: -37
Study 461	HBeAg positive/ compensated liver disease Lamivudine monotherapy (n=19) ADV monotherapy (n=19) ADV + ongoing LAM (n=20)	 8.2 8.4 7.9	 0.0 -2.86[b] -2.87[b]	Study ongoing[d]	 101 73.5	 -18[b] -15[b]	Study ongoing[d]
Study 465	HBeAg positive and HBeAg negative/decompensated liver disease (stratum B, n=39)	8.4	-3.9	Study ongoing[d]	80	-42	Study ongoing[d]
Study 460i	Co-infected with HIV (n=35)	8.64[c]	-3.40[c]	-4.07[c, e]	102.5	Not reported	-16

Note: Efficacy results are for NDA-reported analyses with the exception of study 435 for which results are the updated efficacy analysis (Safety Update Report).

a Results include data for subcohort 2 who were previously treated with adefovir dipivoxil and had suppressed HBV DNA and reduced ALT levels at baseline.

b Results are shown for change at week 16, the primary endpoint in this study.

c Mean values.

d Data now available for week 48 timepoint.

e Data now available for week 96 timepoint.

6. SAFETY EVALUATION

6.1. Extent of Exposure

Clinical trial experience in a substantial population was presented in the NDA to support the safety assessment of adefovir dipivoxil 10 mg once daily in the proposed indication. Through December 31, 2001 (safety cutoff for NDA submission), 1,517 patients with chronic hepatitis B, non-HBV infected patients, and healthy volunteers had received adefovir dipivoxil at the recommended dose of 10 mg daily for varying lengths of exposure in studies in the clinical development program. The safety update contained analyses of targeted safety parameters on 492 patients from two phase 3 placebo-controlled clinical studies of adefovir dipivoxil 10 mg daily (GS-98-437, GS-98-438) and from an open-label study of 324 patients either waitlisted for liver transplantation or post-liver transplantation with lamivudine-resistant chronic hepatitis B (GS-98-435). Demographics, study drug termination, exposure to adefovir dipivoxil 10 mg, serious adverse events, and laboratory data were summarized and analyzed in the NDA Safety Update. In the following sections, data from the safety update is presented where available. In all other sections data is presented from the original NDA.

The safety experience described in the Integrated Summary of Safety (ISS) for the NDA included 523 patients who had received treatment with adefovir dipivoxil 10 mg daily for ≥ 48 weeks, including 316 patients treated for ≥ 72 weeks and 70 patients treated for ≥ 96 weeks.

Safety data from an open-labeled study where adefovir dipivoxil was added to ongoing lamivudine in patients with lamivudine-resistant chronic HBV, post-liver transplantation cohort in study 435 (n = 131) were also provided in the ISS to support the safety of adefovir dipivoxil 10 mg. In addition, information on deaths and serious adverse events for patients waitlisted for liver transplantation in study 435, and safety data for patients in other supportive studies and extension studies of the pivotal studies were also provided (studies 461, 460i and 465).

As of February 28, 2002 (safety cutoff for NDA 21-449 Safety Update), the total number of patients exposed to adefovir dipivoxil 10 mg daily reached 816 patients.

The number of patients in the phase 3 studies of adefovir dipivoxil (i.e., integrated safety population for studies 437 and 438, and the liver transplantation population of study 435) reported in the NDA ISS and the Safety Update Report by duration of treatment are summarized in Table 12.

Table 12. Exposure to Adefovir Dipivoxil 10 mg in Phase 3 Clinical Studies

Study/ Submission	Treatment Group	No. Treated With ADV*	Weeks on Study Medication	
			Median	Maximum
Studies 437/438				
NDA	ADV 10 mg (0-48 weeks)	294	48	50.0
	All ADV 10 mg**	492	48	91.7
Safety Update	ADV 10 mg → ADV 10 mg	164	88.1	109.4
	ADV 10 mg → placebo	111	48.4	84.9
	Placebo → ADV 10 mg	198	34.6	64.0
	All ADV 10 mg**	492	49.0	109.4
Supportive Study				
Study 435				
NDA	Post-Transplantation (Cohort A)	131	32.8	88.1
Safety Update	Post-Transplantation (Cohort A)	196	56.1	129.3
	Waitlisted (Cohort B)	128	18.7	72.0

Note: exposure based on numbers at cutoff for CRF data.

* In general dosing was at 10 mg once daily except where dose reduction was made according to protocol criteria.

** Includes all patients who received at least one dose of adefovir dipivoxil 10 mg in the first and/or second 48-week treatment period. Data obtained from study visits subsequent to the first randomization/dosing allocation error in year 2 of study 437 are excluded from the ALL ADV 10 mg dataset.

6.2. Results of Integrated Safety Analyses (Combined Studies 437 and 438)

Adefovir dipivoxil 10 mg once daily is the proposed dose for regulatory approval. To support this dosing regimen, the frequencies of adverse events and laboratory abnormalities reported in the NDA safety analyses that compare adefovir dipivoxil 10 mg and placebo during the first double-blind, 48-weeks of treatment in studies 437 and 438 (integrated safety population) are first summarized in this Safety Section. Adverse event data from patients randomized to adefovir dipivoxil 30 mg daily in year 1 of study 437 are provided in Appendix 3. Safety information with respect to deaths, serious adverse events (SAEs), and discontinuations due to adverse events in the integrated 437/438 safety population are reviewed as reported in the Safety Update Report. Targeted evaluations of renal laboratory abnormalities and ALT elevations are also provided in this section for the integrated 437/438 dataset.

6.2.1. NDA Analysis (Adefovir Dipivoxil 10 mg versus Placebo): Adverse Events and Laboratory Abnormalities

Adverse Events:

Overall, the nature, frequency and severity of adverse events during the first 48 weeks of treatment in studies 437 and 438 were similar between the adefovir dipivoxil 10 mg and placebo groups. The most common adverse events were headache, pharyngitis, asthenia, abdominal pain, and flu syndrome. The vast majority of adverse events were of mild (grade 1) or moderate (grade 2) severity (based on the Gilead Sciences Toxicity Grading Scale). Summaries of frequent adverse events (incidence of ≥ 3% in the All adefovir dipivoxil 10 mg group) and grade 3 or higher adverse events (reported in ≥ 2 patients in the All adefovir dipivoxil 10 mg group) are included in Appendix 5 (Table 5-1 and 5-2). Related adverse events (grades 1 to 4) reported with a frequency of ≥ 1% in the All adefovir dipivoxil 10 mg group are summarized in Table 13.

Table 13. Treatment-Related Adverse Events (Grades 1-4) Reported in ≥ 1% of Patients in the All Adefovir Dipivoxil 10 mg Group: Studies 437 and 438 (NDA Cutoff)

	Placebo (0-48 Weeks) (N = 228)		ADV 10 mg (0-48 Weeks) (N = 294)		All ADV 10 mg (0-96 Weeks) (N = 492)	
Adverse Event	n	(%)	n	(%)	n	(%)
Number of Patients with Related Adverse Events	115	(50%)	132	(45%)	175	(36%)
Asthenia	33	(14%)	39	(13%)	49	(10%)
Headache	23	(10%)	27	(9%)	38	(8%)
Abdominal Pain	24	(11%)	27	(9%)	37	(8%)
Nausea	19	(8%)	16	(5%)	21	(4%)
ALT Increased	10	(4%)	7	(2%)	11	(2%)
Flatulence	9	(4%)	11	(4%)	11	(2%)
Anorexia	9	(4%)	7	(2%)	9	(2%)
Creatinine Increased	1	(<1%)	7	(2%)	9	(2%)
Diarrhea	8	(4%)	8	(3%)	9	(2%)
Dizziness	7	(3%)	7	(2%)	9	(2%)
Dyspepsia	5	(2%)	9	(3%)	9	(2%)
Insomnia	6	(3%)	4	(1%)	9	(2%)
Somnolence	10	(4%)	6	(2%)	9	(2%)
Carnitine Decreased	1	(<1%)	6	(2%)	8	(2%)
Pruritus	8	(4%)	5	(2%)	8	(2%)
Hypophosphatemia	3	(1%)	5	(2%)	7	(1%)
Liver Function Tests Abnormal	6	(3%)	4	(1%)	7	(1%)
Myalgia	7	(3%)	5	(2%)	6	(1%)
Pain	6	(3%)	5	(2%)	6	(1%)
Vomiting	3	(1%)	4	(1%)	6	(1%)
Alopecia	2	(<1%)	3	(1%)	5	(1%)
Back Pain	3	(1%)	5	(2%)	5	(1%)
Depression	4	(2%)	4	(1%)	5	(1%)
Rash	9	(4%)	3	(1%)	5	(1%)
Rhinitis	5	(2%)	4	(1%)	5	(1%)

Note: Related = possible, probable or unassessable relationship to treatment as assessed by the investigator.

None of the more frequent related adverse events (i.e., asthenia, headache, abdominal pain, nausea, flatulence, diarrhea and dyspepsia) led to study drug discontinuations. The incidences of these events between the adefovir dipivoxil 10 mg and placebo groups were similar. Only a very small number of related adverse events were assessed as severe (≥ grade 3); reported in 7 patients (3%) in the placebo group, 10 patients (3%) in the adefovir dipivoxil 10 mg, and 12 patients (2%) in the All adefovir dipivoxil 10 mg group. ALT elevation was the most common of these events, occurring in 5 (2%), 3 (1%), and 3 (< 1%) of the placebo, adefovir dipivoxil 10 mg, and All adefovir dipivoxil 10 mg groups, respectively.

Laboratory Parameters:

Hematology, serum chemistry, and urinalysis parameters that were measured during the course of treatment were investigated with respect to changes from baseline and the incidence of abnormalities by toxicity grade based on the Gilead Sciences Toxicity Grading Scale. Summary tables for these analyses are provided in Appendix 5 (Tables 6-3 and 6-4).

This detailed assessment revealed no clinically relevant differences related to safety between the adefovir dipivoxil 10 mg group and the placebo group during the first 48 weeks of double-blind treatment. The only notable differences in the evaluation of laboratory parameters between the adefovir dipivoxil 10 mg and placebo was in relation to decreases in ALT that were associated with treatment with adefovir dipivoxil 10 mg.

A marked laboratory abnormality was defined as a shift from grade 0 at baseline to at least grade 3 during study or from grade 1 at baseline to grade 4 during study. Marked laboratory changes occurred infrequently during the first 48 weeks of double-blind treatment and among all patients who received at least 1 dose of adefovir dipivoxil 10 mg up to 92 weeks (Table 14). There were no notable differences in marked laboratory abnormalities between the adefovir dipivoxil 10 mg and placebo groups, with the exception of higher incidence of marked ALT and AST abnormalities in the placebo group.

Table 14. Grade 3-4 Laboratory Abnormalities: Studies 437 and 438 (NDA Cutoff)

	Placebo (0-48 Weeks) (N = 228)		ADV 10 mg (0-48 Weeks) (N = 294)		All ADV 10 mg (0-96 Weeks) (N = 492)	
	n	(%)	n	(%)	N	(%)
ALT Elevation	11/228	(5%)	4/293	(1%)	9/490	(2%)
AST Elevation	9/228	(4%)	2/293	(<1%)	5/490	(1%)
GGT Elevation	1/228	(<1%)	0	(0%)	1/491	(<1%)
Serum Amylase Elevation	3/220	(1%)	0	(0%)	2/491	(<1%)
Hyponatremia	1/228	(<1%)	4/293	(1%)	4/491	(<1%)
Hypernatremia	0/228	(0%)	0/293	(0%)	2/491	(<1%)
Hypocalcemia	1/228	(<1%)	2/293	(<1%)	2/491	(<1%)
Hyperglycemia	0/228	(0%)	1/293	(<1%)	1/490	(<1%)
Hypophosphatemia	0/228	(0%)	1/293	(<1%)	1/491	(<1%)
Creatine Kinase Elevation	14/228	(6%)	18/293	(6%)	23/490	(5%)
Decreased Platelets	0/224	(0%)	0/289	(0%)	3/437	(<1%)
Prolonged Prothrombin Time	0/225	(0%)	1/289	(<1%)	1/487	(<1%)
Decreased Neutrophils	0/226	(0%)	0/293	(0%)	1/449	(<1%)
Glycosuria	2/228	(<1%)	3/293	(1%)	8/490	(2%)
Hematuria	15/194	(8%)	16/260	(6%)	22/457	(5%)

Note: Marked laboratory toxicity are defined as a shift from grade 0 at baseline to at least grade 3 during study or from grade 1 at baseline to grade 4 during study.

6.2.2. Safety Update Analysis: Deaths, SAEs, and Discontinuations Due to Adverse Events

As of February 28, 2002, a cumulative total of three patients have died in the integrated studies (2 patients in study 437 and one in study 438). Two of the deaths were assessed as unrelated to treatment (T-cell lymphoma and mycosis septicemia). The third death was a case of cardiac arrest where the investigator was not able to completely exclude ADV as a contributory factor and the patient did have underlying cardiomyopathy.

The overall incidence of serious adverse events for all patients exposed to adefovir dipivoxil 10 mg was 5%; the incidences for each of the three randomized groups did not appreciably differ from one another (Table 15). No single type of SAE occurred in more than 2 of the total of 492 patients (< 1%) exposed to adefovir dipivoxil 10 mg, or in more than 1 patient in each of the three randomized groups.

Table 15. All Serious Adverse Events: Studies 437 and 438 (Safety Update Cutoff)

	ADV 10 mg ⟶ ADV 10 mg (N = 164		ADV 10 mg ⟶ Placebo (N = 111)		Placebo ⟶ ADV 10 mg (N = 198)		All ADV 10 mg (N = 492)	
Number with Any Event	8	(5%)	7	(6%)	6	(3%)	27	(5%)
Abdominal Pain	1	(< 1%)	0	(0%)	1	(< 1%)	2	(< 1%)
Accidental Injury	0	(0%)	0	(0%)	1	(< 1%)	2	(< 1%)
Chest Pain	0	(0%)	2	(2%)	0	(0%)	2	(< 1%)
Depression	0	(0%)	2	(2%)	0	(0%)	2	(< 1%)
Kidney Pain	1	(< 1%)	0	(0%)	1	(< 1%)	2	(< 1%)
Viral Infection	0	(0%)	0	(0%)	0	(0%)	2	(< 1%)
Abscess	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Ascites	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Cerebrovascular Accident	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Coagulation Disorder	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Confusion	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Coronary Artery Disorder	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Creatinine Phosphokinase Increased	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Edema	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Fracture	0	(0%)	0	(0%)	1	(< 1%)	1	(< 1%)
Gastrointestinal Hemorrhage	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Headache	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Hematuria	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)
Liver Function Tests Abnormal	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Meningism	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Neuropathy	0	(0%)	0	(0%)	1	(< 1%)	1	(< 1%)
Rash	0	(0%)	0	(0%)	1	(< 1%)	1	(< 1%)
Otitis Media	0	(0%)	0	(0%)	1	(< 1%)	1	(< 1%)
Parathyroid Disorder	0	(0%)	0	(0%)	1	(< 1%)	1	(< 1%)
SGOT (AST) Increased	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)
SGPT (ALT) Increased	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)
Urinary Incontinence	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Weight Loss	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)

The incidence of adverse events leading to study drug discontinuation for all patients exposed to adefovir dipivoxil 10 mg was 3 (Table 16).

Table 16. Adverse Events Leading to Study Drug Discontinuation: Studies 437 and 438 (Safety Update Cutoff)

	ADV 10 mg → ADV 10 mg (N = 164)		ADV 10 mg → Placebo (N = 111)		Placebo → ADV 10 mg (N = 198)		All ADV 10 mg N = 492)	
Number of Patients with Any Event	4	(2%)	5	(5%)	2	(1%)	16	(3%)
SGPT (ALT) Increased	1	(< 1%)	2	(2%)	1	(< 1%)	5	(1%)
Liver Function Tests Abnormal	1	(< 1%)	1	(< 1%)	1	(< 1%)	4	(< 1%)
GGT Increased	0	(0%)	1	(< 1%)	1	(< 1%)	2	(< 1%)
SGOT (AST) Increased	0	(0%)	1	(< 1%)	0	(0%)	2	(< 1%)
Amnesia	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Hepatoma	1	(< 1)	0	(0%)	0	(0%)	1	(< 1%)
HIV Test Positive	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)
Jaundice	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Meningism	1	(< 1%)	0	(0%)	0	(0%)	1	(< 1%)
Maculopapular Rash	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)
Nausea	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Pruritus	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)
Skin Disorder	0	(0%)	1	(< 1%)	0	(0%)	1	(< 1%)
Weight Loss	0	(0%)	0	(0%)	0	(0%)	1	(< 1%)

In summary, low incidences of serious adverse events (5%) and adverse events leading to drug discontinuation (3%) were observed.

6.2.3. Targeted Evaluation of Renal Laboratory Parameters

In preclinical studies, evidence of renal toxicity was noted in all species investigated at doses of adefovir dipivoxil producing systemic exposures approximately 3 to 10 times that in humans at the recommended therapeutic dose for chronic hepatitis B of 10 mg daily. Clinically, at daily doses of 30 mg to 120 mg, nephrotoxicity is the most important dose-limiting toxicity of adefovir dipivoxil therapy. This toxicity has been characterized using data from both HIV-infected and chronic hepatitis B patients treated with doses 3 to 12 times higher (up to 120 mg daily) than the recommended 10 mg daily dose. Nephrotoxicity was primarily manifested by the onset of gradual increases in serum creatinine and decreases in serum phosphorus, with a delayed onset generally after

20 weeks or more of therapy with a median of 28-36 weeks with doses of adefovir dipivoxil 30 mg or greater daily (studies 437, 417, and 408). These changes were usually mild to moderate in severity and in some patients were accompanied by changes in serum bicarbonate, glycosuria, and proteinuria. Analyses of these changes revealed that an increase from baseline in serum creatinine of ≥ 0.5 mg/dL or a decrease from baseline in serum phosphorus to < 1.5 mg/dL were the most sensitive and specific indicators of adefovir-related nephrotoxicity. Consequently, these changes were used in the study toxicity management guidelines to identify patients who should be permanently discontinued from study medication.

Further assessment of the renal profile at higher doses (≥ 30 mg) of adefovir dipivoxil is provided in Appendix 6.

Assessment of the renal effects of adefovir dipivoxil 10 mg is based principally on the incidence of increases in serum creatinine and decreases in serum phosphorus in the integrated safety population (studies 437 and 438). Data for other laboratory abnormalities, i.e., proteinuria, glycosuria, hematuria, and decreased serum bicarbonate, are also summarized, although these are considered less specific markers of adefovir-related renal tubular dysfunction.

As described below, there was no evidence of nephrotoxicity in the integrated safety population of studies 437 and 438 treated with adefovir dipivoxil 10 mg for up to 48 weeks.

NDA Analysis (Placebo-Controlled):

There were no clinically relevant changes (as evidenced by median changes) in serum creatinine or serum phosphorus from baseline following 48 weeks of treatment with adefovir dipivoxil 10 mg (Appendix 5, Table 5-3). Specifically, there was no median change in serum creatinine from baseline and there was a median increase in serum phosphorus from baseline of 0.05 mg/dL in the adefovir dipivoxil 10 mg group compared with 0.1 mg/dL in the placebo group.

- At entry into the study the exclusion criteria relating to serum creatinine allowed patients with grade 1 serum creatinine abnormalities to enter the protocol. There were very few graded abnormalities for serum creatinine or serum phosphorus throughout the 48-week treatment period and no differences between adefovir dipivoxil and placebo (Table 17). Ninety-nine percent of patients in the adefovir dipivoxil 10 mg (0-48 weeks) and in the All adefovir dipivoxil 10 mg (0-96 weeks) groups had serum creatinine levels within the normal range throughout the study. Three patients had a grade 1, and one patient had a grade 2 serum creatinine elevation in the All adefovir 10 mg group, but these abnormalities were not confirmed on repeat laboratory test. Grade 3 or 4 serum creatinine elevation was not observed in any group. Most patients had normal serum phosphorus levels during treatment. Of patients with grade 2 hypophosphatemia, similar incidences were reported in the placebo (4%), adefovir dipivoxil 10 mg (3%), and All adefovir dipivoxil 10 mg (3%) groups. One grade 3

hypophosphatemia was reported in the adefovir dipivoxil 10 mg group, but it was not confirmed on repeat laboratory testing.

Table 17. Assessment of Renal Function, Incidence of Maximum Grade of Serum Laboratory Abnormality: Studies 437 and 438 (NDA Cutoff)

Laboratory Parameter/ Grade of Toxicity	Placebo (0-48 Weeks)		ADV 10 mg (0-48 Weeks)		All ADV 10 mg (0-96 Weeks)	
	n/N	%	n/N	%	n/N	%
Creatinine (mg/dL)						
1 1.5–2.0	0/228	(0%)	3/293	(1%)	3/491	(< 1%)
2 2.1–3.0	0/228	(0%)	0/293	(0%)	1/491	(< 1%)
3 3.1–6.0	0/228	(0%)	0/293	(0%)	0/491	(0%)
4 > 6.0	0/228	(0%)	0/293	(0%)	0/491	(0%)
Hypophosphatemia (mg/dL)						
1 2.0–2.2	9/228	(4%)	12/293	(4%)	22/491	(4%)
2 1.5–1.9	10/228	(4%)	8/293	(3%)	15/491	(3%)
3 1.0–1.4	0/228	(0%)	1/293	(< 1%)	1/491	(< 1%)
4 < 1.0	0/228	(0%)	0/293	(0%)	0/491	(0%)
Decreased serum bicarbonate (mEq/L)						
1 (16–< 17 mEq/L)	2/228	(<1%)	4/293	(1%)	6/490	(1%)
2 (11–15.9 mEq/L)	0/228	(0%)	3/293	(0%)	4/490	(< 1%)
3 (8–10.9 mEq/L)	0/228	(0%)	0/293	(0%)	0/490	(0%)
4 (< 8 mEq/L)	0/228	(0%)	0/293	(0%)	0/490	(0%)

- There were low incidences of abnormalities for other indicators of renal dysfunction. The incidence of decreased serum bicarbonate is shown in Table 17 and incidences of glycosuria, proteinuria, and hematuria in Table 18.

Table 18. Assessment of Renal Function, Incidence of Maximum Grade of Urine Laboratory Abnormality: Studies 437 and 438 (NDA Cutoff)

Laboratory Parameter/ Grade of Toxicity	Placebo (0-48 Weeks)		ADV 10 mg (0-48 Weeks)		All ADV 10 mg (0-96 Weeks)	
	n/N	%	n/N	%	n/N	%
Glycosuria						
1 1+	7/228	(3%)	2/293	(< 1%)	7/490	(1%)
2 2+	4/228	(2%)	3/293	(1%)	2/490	(< 1%)
3 3+	6/228	(3%)	4/293	(1%)	9/490	(2%)
4 4	0/228	(0%)	0/293	(0%)	0/490	(0%)
Hematuria						
1 < 10 RBCs	22/227	(10%)	26/293	(9%)	37/490	(8%)
2 10–100 RBCs	25/227	(11%)	32/293	(11%)	50/490	(10%)
3 > 100 RBCs	23/227	(10%)	31/293	(11%)	42/490	(9%)
4 Obstructive	0/227	(0%)	0/293	(0%)	0/490	(0%)
Proteinuria (mg/dL)						
1 1+	24/228	(11%)	39/293	(13%)	51/490	(10%)
2 2+ to 3+	12/228	(5%)	17/293	(6%)	24/490	(5%)
3 4+	0/228	(0%)	0/293	(0%)	0/490	(0%)
4 Nephrotic syndrome	0/228	(0%)	0/293	(0%)	0/490	(0%)

- The original protocols for study GS-98-437 (n = 515) and study GS-98-438 (n = 185) included uniform adefovir dipivoxil (ADV) management guidelines that required dose reduction for patients who experienced a confirmed (defined as 2 consecutive laboratory assessments) increase in serum creatinine of ≥ 0.3 mg/dL from baseline. Patients who experienced a confirmed increase in serum creatinine ≥ 0.3 mg/dL above baseline were dose interrupted until resolution to within 0.3 mg/dL above baseline and then were allowed to resume dosing at a reduced dose. Patients who were randomized to receive either ADV 30 mg or 10 mg were reassigned upon dose reduction to receive ADV 10 mg or 5 mg in a blinded fashion. Patients who were randomized to receive placebo (PLB) continued to receive PLB. Upon guidance from the Agency given at the end of phase 2 meeting in April 2000, which was endorsed by the independent and external Data Monitoring Committee in May 2000, both protocols were amended in September 2000. The amendment eliminated the dose reduction strategy to enable a clearer assessment of the incidence of nephrotoxicity and subsequent resolution. The subsequent amended protocol toxicity management guidelines required patients to discontinue study medication permanently in the event that they experienced an increase in serum creatinine of ≥ 0.5 mg/dL from baseline and confirmed by 2 consecutive laboratory abnormalities. Changes in renal function

as evidenced by serum creatinine ≥ 0.5 mg/dL from baseline and/or serum phosphorus < 1.5 mg/dL, as confirmed by two consecutive laboratory assessments, were not observed in patients treated with adefovir dipivoxil 10 mg for at least 48 weeks. One patient in the placebo group and 4 patients in the adefovir dipivoxil 10 mg group had an unconfirmed increase in serum creatinine ≥ 0.5 mg/dL from baseline; none of these events were confirmed on repeat testing, and by the next study visit (while on study drug) all resolved to ≤ 0.3 mg/dL from baseline. Similarly, one serum phosphorus of < 1.5 mg/dL that occurred in an adefovir dipivoxil patient was not confirmed upon repeat laboratory assessment.

In order to more thoroughly assess the effects of adefovir dipivoxil 10 mg on serum creatinine and serum phosphorus, Gilead performed more conservative analyses evaluating lower renal thresholds that would identify the number of patients showing increases in serum creatinine (≤ 0.3 mg/dL) and reductions in serum phosphorus (< 2.0 mg/dL).

- In study GS-98-437, the Kaplan-Meier (KM) estimates for the incidence of confirmed increases in serum creatinine of ≥ 0.3 mg/dL from baseline by week 48 were 1%, 5%, and 42% for the PLB, ADV 10 mg and ADV 30 mg groups respectively (see Table 1). The KM estimates for the incidence of resolution of increased serum creatinine to ≤ 0.2 mg/dL by week 48 post event were 0%, 80%, and 78% in the PLB, ADV 10 mg and ADV 30 mg groups respectively. None of the PLB group (n = 170) was dose reduced. Five of the nine patients in the ADV 10 mg group (n = 172) and 38 of 69 patients (55%) in the ADV 30 mg group (n = 173) who had an increase of ≥ 0.3 mg/dL respectively were dose reduced. The remaining patients continued to take the original dose.

- In study GS-98-438, the KM estimates for the incidence of confirmed increases in serum creatinine of ≥ 0.3 mg/dL from baseline by week 48 were 5% and 2% for the PLB and ADV 10 mg groups respectively (see Table 19). The KM estimates for the incidence of resolution of increased serum creatinine to ≤ 0.2 mg/dL by week 48 were 100% and 67% in the PLB and ADV 10 mg groups respectively. No patients in the PLB group (n = 62) and one patient in the ADV 10 mg group (n = 123) who had an increase of ≥ 0.3 mg/dL were dose reduced. The remaining patients continued to take the original dose.

- In Integrated Analysis (studies GS-98-437 and GS-98-438), the KM estimates for the incidence of confirmed increases in serum creatinine of ≥ 0.3 mg/dL from baseline by week 48 for both studies combined were 2% and 4% for the PLB (n = 228) and ADV 10 mg (n = 294) groups respectively (see Table 19). The KM estimates for the incidence of resolution of increased serum creatinine to ≤ 0.2 mg/dL by week 48 were 75% and 82% in the PLB and ADV 10 mg groups respectively.

- In study GS-98-437, the incidence of confirmed serum phosphorus of < 2.0 mg/dL in study GS-98-437 was 1%, 0%, and 5% for the PLB (n = 170), ADV 10 mg (n = 172) and ADV 30 mg (n = 173) groups respectively (see Table 20). The KM estimates for the incidence of resolution of serum phosphorus to ≥ 2.0 mg/dL by week 48 were 100% and 100% in the PLB and ADV 30 mg groups respectively. No patients in the PLB group who had a confirmed serum phosphorus < 2.0 mg/dL required phosphorus supplementation. Six patients in the ADV 30 mg groups received phosphorus supplementation.

- In study GS-98-438, the incidence of confirmed serum phosphorus of < 2.0 mg/dL in study GS-98-438 was 0% and 0% for the placebo and ADV 10 mg groups respectively (see Table 20). No patients required phosphorus supplementation in the PLB or ADV 10 mg group.

- In the Integrated Analysis (studies GS-98-437 and GS-98-438), the incidence of confirmed serum phosphorus of < 2.0 mg/dL in study GS-98-438 by week 48 for both studies combined was 1% and 0% for the PLB (n = 228) and ADV 10 mg (n = 294) groups respectively (see Table 20).

Overall, based on the integrated analyses of studies GS-98-437 and GS-98-438, the incidence of confirmed serum creatinine ≥ 0.3 mg/dL elevations from baseline in the ADV 10 mg group appear to be similar to PLB. Although there is a slightly higher incidence in study GS-98-437, the reverse is seen in study GS-98-438. Study GS-98-438, where only one ADV 10 mg patient was dose reduced, provides a better evaluation of the impact of an increase of ≥ 0.3 mg/dL in serum creatinine as for the greater part of this study the protocol defined toxicity management guidelines did not require a dose reduction. This allowed us to evaluate whether continued dosing would result in further increases in serum creatinine beyond 0.3 mg/dL.

In conclusion, as there appears to be no difference between ADV 10 mg and PLB in the incidence of increased serum creatinine at this level, a confirmed increase of ≥ 0.5 mg/dL is associated with a lower false positive rate and is therefore a more appropriate endpoint.

Table 19. Confirmed Serum Creatinine ≥ 0.3 mg/dL from Baseline

	No. of Patients (K-M Estimates)	Resolution			
	Confirmed Serum Creatinine ≥ 0.3 mg/dL from BL		No. Patients Resolved*/ Unresolved by 48 Weeks	Continued at Full Dose	With Dose Reduction
Study 437 PLB (n = 170)	1 (1%)	Resolved	0 (0%)	0	0
		Unresolved	1	1	0
Study 437 ADV 10 mg (n = 172)	9 (5%)	Resolved	6 (80%)	4	2
		Unresolved	3	0	3
Study 437 ADV 30 mg (n = 173)	69 (42%)	Resolved	42 (61%)	18	24
		Unresolved	27	13	14
Study 438 PLB (n = 62)	3 (5%)	Resolved	3 (100%)	3	0
		Unresolved	0	0	0
Study 438 ADV 10 mg (n = 123)	3 (2%)	Resolved	2 (67%)	2	0
		Unresolved	1	0	1
Integrated PLB (n = 228)	4 (2%)	Resolved	3 (75%)	3	0
		Unresolved	1	1	0
Integrated ADV 10 mg (n = 294)	12 (4%)	Resolved	8 (82%)	6	2
		Unresolved	4	0	4

* Resolved defined as serum creatinine ≤ 0.2 mg/dL from baseline

Table 20. Confirmed Serum Phosphorus < 2.0 mg/dL

	No. of Patients (K-M Estimates)	
	Confirmed Serum Phosphorus < 2.0 mg/dL	**Resolution to ≥ 2.0 mg/dL by 48 Weeks Post Event**
Study 437 PLB (n = 170)	2 (1%)	2 (100%) (both with Full Dose; no supplementation required)
Study 437 ADV 10 mg (n = 172)	0 (0%)	NA
Study 437 ADV 30 mg (n = 173)	9 (5%)	9 (100%)
		(6/9 required phosphate supplementation) 4/9 resolved with Reduced Dose 3/9 resolved with Full Dose 2/9 resolved with Interruption or Drug Discontinuation
Study 438 PLB (n = 62)	0 (0%)	NA
Study 438 ADV 10 mg (n = 123)	0 (0%)	NA
Integrated PLB (n = 228)	2 (1%)	2 (100%) (both with Full Dose; no supplementation required)
Integrated ADV 10 mg (n = 294)	0 (0%)	NA

Safety Update Analysis:

- Further support for the lack of nephrotoxicity is provided by the results of the Safety Update analysis. At 96 weeks, confirmed serum creatinine increase ≥ 0.5 mg/dL from baseline was reported in 2 of 492 (< 1%) patients in the All adefovir dipivoxil group treated for a median of 49 weeks up to a maximum of 109 weeks (see Appendix 6). Both abnormalities were reported in the adefovir dipivoxil 10 mg → adefovir dipivoxil 10 mg group. One patient with baseline serum creatinine of 1.0 mg/dL had an increase > 0.5 mg/dL from baseline at week 80 to a maximum level of 2.3 mg/dL (confirmed at 1.6 mg/dL); resolution to ≤ 0.3 mg/dL from baseline was observed at the next study visit (week 84) following discontinuation of drug. The second patient had a serum creatinine increase from 0.6 mg/dL (57 µmol/L) at baseline (screening 0.7 mg/dL) to 1.1 mg/dL (96 µmol/L in SI units) at week 88. This event was confirmed at week 92 only by conventional units (0.5 mg/dL increase from baseline), but not by SI units (39 µmol/L increase from baseline) so drug discontinuation was not required as the patient was managed at an ex-US site using SI units. Resolution to ≤ 0.3 mg/dL from baseline was

observed at week 104 with continued adefovir dipivoxil dosing. There were no patients with confirmed serum phosphorus < 1.5 mg/dL in the Safety Update analysis.

In conclusion, the results of the assessment of renal laboratory data demonstrate no current evidence of the emergence of nephrotoxicity at the 10 mg dose of adefovir dipivoxil in patients with chronic hepatitis B.

6.2.4. Targeted Evaluation of ALT Elevations

NDA Analysis (Placebo-Controlled):

In the integrated safety analysis, significant increases (> 5 x ULN) in ALT were less frequently encountered in the adefovir dipivoxil 10 mg group compared with the placebo group (41% had grade 3 or 4 ALT elevation in the placebo group compared with 20% in the adefovir dipivoxil 10 mg group). This is a consequence of the clinical benefit of antiviral treatment. Large elevations in serum ALT associated with drug-related hepatic toxicity generally occur with concurrent changes in bilirubin, albumin, and prothrombin time. As shown in Table 21, ALT elevations (> 10 x ULN) with concurrent abnormalities were not observed in patients treated with adefovir dipivoxil 10 mg for up to 92 weeks.

Table 21. ALT Abnormalities with Concurrent Changes in Bilirubin, Albumin, Prothrombin Time and HBV DNA: Studies 437 and 438 (NDA Cutoff)

	Placebo (0-48 Weeks) (N = 228)		ADV 10 mg (0-48 Weeks) (N = 294)		All ADV 10 mg (0-96 Weeks) (N = 492)	
	n	(%)	N	(%)	N	(%)
> 5 to 10 ULN	55	(24%)	40	(14%)	64	(13%)
Bilirubin ≥ 2.5 mg/dL and ≥ 1 mg/dL above baseline	1	(<1%)	0	(0%)	1	(<1%)
Albumin < 3.0 mg/dL	1	(<1%)	0	(0%)	1	(<1%)
Prothrombin time prolonged ≥ 1.5 sec	0	(0%)	0	(0%)	0	(0%)
HBV DNA < 400 copies/mL	0	(0%)	1	(<1%)	3	(<1%)
> 10 to 20 x ULN	32	(14%)	17	(6%)	23	(5%)
Bilirubin ≥ 2.5 mg/dL and ≥ 1 mg/dL above baseline	1	(<1%)	0	(0%)	0	(0%)
Albumin < 3.0 mg/dL	2	(<1%)	0	(0%)	0	(0%)
Prothrombin time prolonged ≥ 1.5 sec	0	(0%)	0	(0%)	0	(0%)
HBV DNA < 400 copies/mL	0	(0%)	2	(<1%)	3	(<1%)
> 20 x ULN	7	(3%)	2	(<1%)	2	(<1%)
Bilirubin ≥ 2.5 mg/dL and ≥ 1 mg/dL above baseline	3	(1%)	0	(0%)	0	(0%)
Albumin < 3.0 mg/dL	0	(0%)	0	(0%)	0	(0%)
Prothrombin time prolonged ≥ 1.5 sec	1	(<1%)	0	(0%)	0	(0%)
HBV DNA < 400 copies/mL	0	(0%)	0	(0%)	0	(0%)

Note: Bilirubin, albumin, and prothrombin time values occurred within ± 35 days of ALT elevation

Safety Update Analysis:

Clinical and laboratory evidence of exacerbations of hepatitis was observed in some patients after discontinuation of adefovir dipivoxil. These exacerbations occurred in the absence of HBeAg seroconversion, and presented as serum ALT elevations, in addition to increases in serum HBV DNA commonly observed after stopping treatment.

The Safety Update analysis demonstrated that patients in the second 48 weeks of 437 and 438 in the adefovir dipivoxil 10 mg → placebo group exhibited both a shift to higher categories of ALT elevation and a greater percentage of patients with elevated bilirubin when switched to placebo in the second 48-week period. This pattern continued into the off-treatment phase after the dosing misallocation in study GS-98-437. For patients off active treatment with ALT elevations > 20 x ULN, 2% of patients also had concurrently elevated bilirubin. When these patients subsequently were switched to open-label adefovir dipivoxil 10 mg, the

incidence of ALT elevations observed was lower than off-treatment incidence, and was consistent with the low rate of ALT elevation during the first 48 weeks of active treatment with adefovir dipivoxil.

These data suggest that withdrawal of effective antiviral treatment with adefovir dipivoxil 10 mg exposes the patient to an increased risk of ALT flare of chronic hepatitis B. Most ALT elevations post-treatment were self-limiting and were not associated with clinical signs of liver decompensation. However, there were a few reports of severe hepatic flares defined as: a confirmed ALT of > 10 × ULN and at least one of the following confirmed laboratory abnormalities:

- Bilirubin ≥ 2.5 mg/dL and > 1.0 mg/dL above baseline
- Albumin < 3.0 g/dL
- Prothrombin time ≥ 1.5 seconds prolonged relative to ULN

For all study phases, 1 (< 1%) patient in the adefovir dipivoxil 10 mg to adefovir dipivoxil 10 mg group experienced severe hepatitis flare, compared with 4 (3%) patients who switched from adefovir dipivoxil 10 mg to placebo in the second 48 weeks. In two cases of post-treatment hepatic flares (ALT > 10 x ULN) that were reported as serious adverse events after the data cutoff date for the Safety Update, both cases were associated with bilirubin elevation and jaundice, but without other clinical signs of liver decompensation. Both cases resolved, one with reinstitution of adefovir dipivoxil therapy and the other with lamivudine treatment.

Therefore, patients who discontinue treatment with adefovir dipivoxil should be monitored closely for a minimum of 12 weeks post-treatment for signs of reactivation of chronic hepatitis B.

6.2.5. Evaluation of Serum Free Carnitine Loss

Dose-related reductions in serum carnitine levels were observed in clinical studies in HIV-infected or HBV/HIV co-infected patients that evaluated doses of adefovir dipivoxil 6 to 25 fold higher than the 10 mg dose intended for treatment of patients with chronic hepatitis B. Decreases in serum free carnitine levels observed at these higher doses in HIV-infected patients were not associated with clinical sequelae when analyzed previously within each individual HIV study and within an integrated safety analysis. Changes in serum free carnitine levels evaluated in study 437 were similar between adefovir dipivoxil 10 mg and placebo treated patients. Therefore, patients will not require routine L-carnitine supplementation or monitoring of serum free carnitine levels when treated with adefovir dipivoxil 10 mg daily.

6.2.6. Integrated Safety Evaluation of Selected Subgroups

Subgroup analyses were conducted on the integrated safety population of patients who received adefovir dipivoxil 10 mg and placebo during the first 48-week double-blind treatment periods of studies 437 and 438. The frequency of adverse events and graded

laboratory toxicities in this pooled population was assessed in subgroups based on age (< 40/≥ 40 years), gender, race (Caucasian, Asian), baseline ALT levels (< 2 x ULN/≥ 2 x ULN) and baseline total Knodell score (< 10/≥ 10). The results of these safety analyses demonstrated no evidence indicative of any clinically important interaction by demographic or baseline disease characteristic.

6.3. Results of Safety Evaluation of Study 435 (Liver Transplantation Patients with Lamivudine-Resistant Chronic Hepatitis B)

Study 435 is an ongoing multicenter, open-label study to evaluate the efficacy and safety of adefovir dipivoxil 10 mg once daily for patients who are either post-liver transplantation or waitlisted for liver transplantation with active liver disease associated with lamivudine-resistant HBV. As described in Section 5.3, post-transplantation patients (cohort A) and waitlisted patients (cohort B) were assigned into one of three study cohorts (1, 2 or 3), based on their renal, hepatic, and hematologic function at baseline and whether they had previously received adefovir dipivoxil through a compassionate use study (study 451i).

The NDA safety evaluation of study 435 was principally based on the Interim Clinical Study Report which describes safety data from 131 cohort A and 25 cohort B patients with median durations of treatment of 33.8 weeks and limited or no post-baseline treatment, respectively. A substantially larger number of patients have been treated in this study for a longer period of follow-up since data cutoff dates for the interim report. The Safety Update Report (submitted to FDA June 2002) reported safety data on 196 cohort A and 128 cohort B patients, with median durations of treatment of 56.1 and 18.7 weeks, respectively. With the exception of the evaluation of frequent adverse events for post-liver transplantation patients (Interim Clinical Study Report), the following sections report more recent data on deaths, serious adverse events, discontinuations due to adverse events and a targeted evaluation of renal parameters based on the updated safety analyses.

6.3.1. Frequent Adverse Events (Post-Liver Transplantation Patients)—NDA Analysis

In post-liver transplantation patients with lamivudine-resistant HBV treated with adefovir dipivoxil 10 mg daily, the most commonly reported adverse events were asthenia, headache, abdominal pain, and pruritus (Table 22).

Most events were of mild or moderate severity, with a total of 34 patients (26%) experiencing at least one grade 3 or 4 adverse event (range from 18% in cohort 1A to 43% in cohort 3A).

Table 22. Adverse Events Reported in ≥ 5% of Patients: Study 435 (Interim Study Report Cutoff)

	1A (N = 79)		2A (N = 10)		3A (N = 42)		Total (N = 131)	
Adverse Event	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**	**N**	**(%)**
Any Adverse Event	55	(70%)	7	(70%)	35	(83%)	97	(74%)
Asthenia	13	(16%)	3	(30%)	6	(14%)	22	(17%)
Headache	12	(15%)	0	(0%)	3	(7%)	15	(11%)
Abdominal Pain	8	(10%)	3	(30%)	2	(5%)	13	(10%)
Pruritus	5	(6%)	1	(10%)	7	(17%)	13	(10%)
Infection	8	(10%)	1	(10%)	3	(7%)	12	(9%)
Fever	5	(6%)	1	(10%)	5	(12%)	11	(8%)
Nausea	8	(10%)	0	(0%)	3	(7%)	11	(8%)
Pain	5	(6%)	2	(20%)	3	(7%)	10	(8%)
Hypertension	7	(9%)	1	(10%)	1	(2%)	9	(7%)
Peripheral Edema	7	(9%)	0	(0%)	2	(5%)	9	(7%)
ALT Increased	7	(9%)	0	(0%)	1	(2%)	8	(6%)
Back Pain	3	(4%)	3	(30%)	2	(5%)	8	(6%)
Flu Syndrome	5	(6%)	2	(20%)	1	(2%)	8	(6%)
Liver Function Test Abnormal	4	(5%)	0	(0%)	4	(10%)	8	(6%)
Pharyngitis	5	(6%)	1	(10%)	2	(5%)	8	(6%)
Vomiting	5	(6%)	0	(0%)	3	(7%)	8	(6%)

6.3.2. Updated Safety Results for Waitlisted and Post-Liver Transplantation Patients

Serious Adverse Events and Deaths

A total of 42 (13%) deaths were reported in cohorts A (18 patients) and B (24 patients). All deaths in cohort A (post-liver transplantation patients) were assessed by the investigator to be due to complications of underlying HBV disease or post-operative complications and not related to adefovir dipivoxil. In cohort B (patients waitlisted for liver transplantation), with the exceptions of multiorgan failure (relationship unknown) and hepatorenal syndrome (possibly related), deaths were assessed by the investigator to be unrelated to treatment.

Overall, there was a low rate of related serious adverse events (5% in cohort A, 4% in cohort B) and adverse events leading to drug discontinuation (5% in cohort A, 6% in cohort B).

In post-liver transplantation patients (cohort A), serious adverse events were reported in 49 patients (25%); events in all but 7 patients were assessed as unrelated to study drug.

In patients waitlisted for liver transplantation (cohort B), serious adverse events were reported in 37 patients (29%); however, 95% of these events were assessed as unrelated to adefovir dipivoxil.

The profile of deaths, SAEs, and discontinuations due to adverse events in this population of liver transplantation patients who were failing lamivudine therapy is consistent with that reported in similar transplantation populations in the presence of recurrent HBV and significant comorbidities.

Targeted Evaluation of Serum Creatinine and Serum Phosphorus

Graded Abnormalities:
In post-liver transplantation patients (cohort A), 41 (21%) of 191 evaluable patients with baseline serum creatinine had a grade 1 or higher baseline serum creatinine, indicative of baseline renal insufficiency in these patients. In these patients, grade 3 or 4 serum creatinine toxicity (serum creatinine ≥ 3.0 mg/dL) was reported in 8 (4%) of 191 evaluable patients; however, 7 of these patients had pre-existing renal insufficiency at baseline (median baseline serum creatinine 2.4 mg/dL, range 1.5 to 5.4 mg/dL). One (1%) patient in cohort 3A had a confirmed serum phosphorus < 1.5 mg/dL (grade 3).

Of the 119 evaluable patients in cohort B (waitlisted for liver transplantation), 7 (6%) had grade 1 or higher serum creatinine at baseline. Grade 3 or 4 serum creatinine toxicity (serum creatinine ≥ 3.0 mg/dL) was reported in 6 (5%) of 119 evaluable patients; however, 3 (50%) of these patients had pre-existing renal insufficiency at baseline (serum creatinine at baseline was grade 3 in 1 patient, grade 4 in two patients). Two (2%) patients waitlisted for liver transplantation had serum phosphorus < 1.5 mg/dL that were not confirmed with two consecutive laboratory assessments.

In summary, while interpretation of these data is complicated, individual patient details demonstrate serum creatinine changes occurred in liver transplantation patients with numerous risk factors for changes in renal function. The changes in renal function may have been due to pre-existing renal disease and/or drug-induced renal dysfunction related to the concomitant immunosuppressant agents or other nephrotoxic drugs. Importantly, a significant proportion of liver transplantation patients with changes in serum creatinine in study 435 would now be managed differently in light of the results of a pharmacokinetic study of adefovir dipivoxil 10 mg in patients with varying degrees of renal impairment (study 473). Results of this study have led to recommendations for dose interval adjustment in patients with moderate to severe renal insufficiency (creatinine clearance < 50 mL/min), as provided in Appendix 2.

Further details of the safety results in study 435 are provided in Appendix 4.

6.3.3. Safety Conclusions for Study 435

Overall, adefovir dipivoxil 10 mg daily was generally well tolerated in this group of 324 severely medically compromised chronic hepatitis B patients who were either waitlisted for or post-liver transplantation with lamivudine-resistant HBV. There was a low incidence of discontinuations due to adverse events and a low incidence of serious related adverse events. Changes in serum creatinine were observed in a proportion of the liver transplantation population with multiple risk factors for changes in renal function. The serum creatinine changes were generally mild in nature and very few patients discontinued due to renal events. In patients waitlisted and post-liver transplantation who are at high risk of disease progression and/or liver graft loss and death if recurrent hepatitis B is not controlled, the new recommendations for dose interval adjustments based on creatinine clearance will allow treatment with adefovir dipivoxil 10 mg to be initiated at an appropriate dose for renal impairment present at baseline, and to be continued with dose interval adjustment in patients with changes in renal function during treatment.

6.4. Safety Experience in Other Populations with Chronic Hepatitis B and Lamivudine-Resistant HBV: Studies 461, 465, and 460i

Available safety data from other supportive ongoing clinical studies in chronic hepatitis B patients with lamivudine-resistant HBV disease (including patients with compensated, decompensated disease and patients co-infected with HIV) confirm an acceptable safety profile for adefovir dipivoxil 10 mg daily and the absence of nephrotoxicity to-date, when administered alone and in combination with lamivudine. The nature, frequency, and severity of adverse events and laboratory abnormalities are consistent with those observed in the integrated phase 3 studies (studies 437 and 438).

6.5. Conclusions of Safety Evaluation

Integrated safety analyses for the two pivotal phase 3 placebo-controlled studies provide clear evidence that adefovir dipivoxil 10 mg once daily is well tolerated in patients with chronic hepatitis B and compensated liver disease during periods of treatment ranging up to 109 weeks. With respect to adverse events and laboratory abnormalities, no differences in the safety profile are evident compared with placebo with the exception of ALT and AST elevations, which occurred much more frequently in the placebo group. Assessment of renal function at week 48 and week 96, demonstrate no evidence of changes in serum creatinine ($\geq$ 0.5 mg/dL) at after 48 weeks and < 1% of patients with changes at 96 weeks. There was no evidence of changes in serum phosphorus. Clinical and laboratory evidence of exacerbations of hepatitis were observed in some patients after discontinuation of adefovir dipivoxil. Therefore, patients who discontinue treatment with adefovir dipivoxil should be monitored post-treatment for signs of reactivation of chronic hepatitis B. The safety profile of adefovir dipivoxil 10 mg in patients with chronic hepatitis B appears similar to that described for lamivudine,[37] and an improvement on interferon-α which has considerable toxicity that frequently results in dose reduction or dose interruption.[7]

Adefovir dipivoxil was generally well tolerated in severely medically compromised chronic hepatitis B patients who were either waitlisted for or post-liver transplantation with

lamivudine-resistant HBV. The safety profile appears comparable to that in published studies of lamivudine in similar populations of liver transplantation patients without lamivudine-resistant HBV, with respect to frequency and nature of serious adverse events and adverse events leading to discontinuation. Changes in serum creatinine were observed in a proportion of liver transplantation patients treated with ADV who had multiple risk factors for changes in renal function. In patients at risk for or with a history of renal dysfunction, routine monitoring of serum creatinine and appropriate dose interval adjustment is recommended. In patients with severe renal insufficiency, consideration should be given to more frequent monitoring of renal function.

7. OVERALL CONCLUSIONS

The principal findings of the clinical development program of adefovir dipivoxil 10 mg once daily in the treatment of chronic hepatitis B are summarized below.

Clinical Efficacy

In two pivotal placebo-controlled studies (studies 437 and 438), adefovir dipivoxil 10 mg was effective when administered to the two principal populations of patients with chronic hepatitis B (HBeAg positive and HBeAg negative) and compensated liver disease:

- Adefovir dipivoxil 10 mg demonstrated statistically significant histological improvement (defined as a reduction of ≥ 2 points from baseline in the Knodell necroinflammatory score with no concurrent worsening in the Knodell fibrosis score) after 48 weeks of treatment. Blinded ranked assessments demonstrated that treatment with adefovir dipivoxil resulted in reductions in both necroinflammation and fibrosis relative to placebo between baseline and week 48 biopsies.

- Histological benefit for adefovir dipivoxil 10 mg relative to placebo was demonstrated regardless of age, gender, race, prior interferon-α treatment, and baseline disease status (assessed according to baseline total Knodell score, baseline serum HBV DNA levels, and baseline ALT levels).

- Significantly greater reductions in serum HBV DNA as determined by the median change from baseline at week 48 and the proportion of patients with HBV DNA < 400 copies/mL (LLQ Roche Amplicor™ PCR) at week 48 were demonstrated for adefovir dipivoxil 10 mg when compared with placebo.

- In addition to the direct antiviral benefit, patients treated with adefovir dipivoxil 10 mg had statistically significant reductions in serum ALT levels and a higher proportion achieved ALT normalization compared with placebo patients.

- In HBeAg positive patients (study 437), a significantly higher proportion of patients treated with adefovir dipivoxil 10 mg compared with placebo achieved HBeAg loss and HBeAg seroconversion.

The efficacy of adefovir dipivoxil 10 mg was also demonstrated in patients with chronic hepatitis B and evidence of lamivudine resistance:

- In chronic hepatitis B patients with lamivudine resistant HBV, treatment with adefovir dipivoxil 10 mg rapidly and significantly reduced serum HBV DNA levels.

- The response was consistent regardless of the pattern of lamivudine-resistant HBV DNA polymerase mutations present at baseline (study 435).

- Antiviral effects were associated with clinical improvement as evidenced by reduction in serum ALT levels, and ALT normalization (studies 435, 460i, 461, 465)

- Improvements in bilirubin albumin and significant improvements in Child-Pugh-Turcotte score (studies 435 and 465) were also observed.

- The survival rates reported for liver transplantation patients appear comparable to survival rates reported in the literature post-liver transplantation patients with HBV treated with HBIg and lamivudine (in patients without lamivudine-resistant HBV mutations) and are greater than survival rates in post-transplantation patients prior to the availability of lamivudine or HBIg and better than survival rates in patients with decompensated cirrhosis (studies 435 and 465).[18, 20, 38]

Populations in the supportive studies included patients with compensated liver disease, patients with decompensated liver disease who are at significant risk of morbidity and mortality, and in patients co-infected with HIV as well as patients pre- and post-liver transplantation. The magnitude of the reductions in serum HBV DNA were similar to those seen in the pivotal studies, studies 437 and 438, indicating similar antiviral efficacy of adefovir dipivoxil 10 mg in all of these patient populations and similar clinical benefit.

Resistance (Results of Genotypic and Phenotypic Analyses)

In the placebo-controlled pivotal phase 3 studies, no HBV DNA polymerase mutations associated with resistance to adefovir were identified in either HBeAg positive or HBeAg negative chronic hepatitis B patients during up to 48 weeks of treatment with adefovir dipivoxil. Furthermore, the results of the phase 2 studies demonstrated that adefovir dipivoxil (5-125 mg) did not lead to the emergence of adefovir resistant mutants of HBV in patients treated with adefovir dipivoxil for up to 136 weeks.

In chronic hepatitis B patients co-infected with HIV, no mutations potentially associated with resistance to adefovir developed in the HBV DNA polymerase of 20 genotyped patients who received 10 mg adefovir dipivoxil daily for 48 weeks. In addition, 48 weeks of 10 mg adefovir dipivoxil daily dosing did not lead to the emergence of the adefovir resistance mutations K65R or K70E in the HIV reverse transcriptase of the 13 genotyped patients.

Clinical Safety

All available clinical data from a substantial population of patients with chronic hepatitis B demonstrate a favorable safety and tolerability profile for adefovir dipivoxil 10 mg once daily. Results of updated safety analysis (NDA Safety Update Report, June 4, 2002) have confirmed the safety profile described in the NDA (March 20, 2002).

In HBeAg positive and HBeAg negative chronic hepatitis B patients with compensated disease, integrated safety analyses demonstrate:

- The nature, incidence, and severity of all adverse events and laboratory abnormalities during the first 48 weeks were similar in the adefovir dipivoxil 10 mg and placebo groups, with the exception of ALT elevations, which were reported in a higher incidence in the placebo group. ALT elevations in the adefovir dipivoxil 10 mg group were not associated with clinical or laboratory evidence of liver decompensation. The incidence of adverse events and laboratory abnormalities did not increase with extended treatment.

- The most commonly reported treatment related adverse events were asthenia, headache, abdominal pain, nausea, flatulence, diarrhea, and dyspepsia. The incidences of these events between the adefovir dipivoxil 10 mg and placebo groups were similar. No patients discontinued adefovir dipivoxil 10 mg for these events.

- Low incidences of serious adverse events (5%) and adverse events leading to drug discontinuation (3%) were reported for patients treated with adefovir dipivoxil 10 mg for up to a maximum of 109 weeks (median 49 weeks).

- At week 48, no patients treated with adefovir dipivoxil 10 mg had a serum creatinine increase of $\geq$ 0.5 mg/dL from baseline or a serum phosphorus < 1.5 mg/dL, as confirmed by two consecutive laboratory assessments. Beyond 48 weeks (n = 492) patients were followed further (median duration of treatment of 88 weeks for adefovir dipivoxil 10 mg $\rightarrow$ adefovir dipivoxil 10 mg), a confirmed serum creatinine increase $\geq$ 0.5 mg/dL from baseline was reported in < 1% patients and no patients had a confirmed serum phosphorus < 1.5 mg/dL. When serum creatinine was further investigated there appeared to be no difference between adefovir dipovixil 10 mg and placebo in the incidence of increased creatinine > 0.3 mg/dL.

In a study of 324 chronic hepatitis B patients who were either waitlisted for or post-liver transplantation with lamivudine-resistant HBV, interim and updated safety analyses demonstrate:

- Adefovir dipivoxil 10 mg daily was generally well tolerated in this group of severely medically compromised patients. The incidence and nature of adverse events were consistent with the advanced disease state of these patients who were failing lamivudine.

- There were few treatment-related serious adverse events and few drug discontinuations due to adverse events. The most commonly reported adverse events were similar to those seen in the integrated studies and included asthenia, headache, abdominal pain, and pruritus.

- In liver transplantation patients with multiple risk factors for changes in renal function including decompensated liver disease, renal dysfunction at baseline and concomitant nephrotoxic immunosuppressant therapy, changes in serum creatinine were observed in a proportion of patients. Serum creatinine increases were generally mild and many patients were able to continue treatment without dose adjustment; 1% of patients discontinued study drug due to a renal event. In these patients who are at high risk of disease progression and/or liver graft loss and death if recurrent hepatitis B is not controlled, the recommendations for dose interval adjustments will allow treatment with adefovir dipivoxil to be initiated at an appropriate dose for renal impairment present at baseline, and to be continued with dose interval adjustment in patients with changes in renal function during treatment.

Supportive safety data from additional studies demonstrate that adefovir dipivoxil 10 mg once daily was well-tolerated in patients with lamivudine-resistant HBV with, compensated or decompensated liver disease, and in patients co-infected with HIV treated for up to 48 weeks.

Overall Conclusion

The information presented in this NDA demonstrate that adefovir dipivoxil 10 mg provides significant histological benefit in patients with chronic hepatitis B, this is supported by antiviral, clinical and immunological, benefits. These effects have been demonstrated in both HBeAg+ and HBeAg-/ anti-HBe+/HBV DNA+ (presumed precore mutant) chronic hepatitis B in patients with compensated liver disease. Adefovir dipivoxil 10 mg also provides similar benefits for patients who have failed lamivudine therapy, including post-OLT patients, patients with compensated or decompensated liver disease and patients with chronic hepatitis B co-infected with HIV. In patients post-liver transplantation or wait-listed for liver transplantation who are at high risk for morbidity and mortality adefovir dipivoxil 10 mg meets an unmet medical need and presents a life-saving treatment option. These benefits are provided with minimal risk of significant adverse effects and with absence of antiviral resistance.

Routine monitoring of serum creatinine is recommended in patients with history of, or at risk for, renal dysfunction for appropriate dose interval adjustment both prior to initiating therapy or during therapy. No notable changes in serum phosphorus were seen, therefore routine monitoring of serum phosphorus during treatment with adefovir dipivoxil is not warranted. Since evidence of exacerbations of hepatitis have been observed in some patients after discontinuation of adefovir dipivoxil, patients should be monitored post-treatment for signs of reactivation of chronic hepatitis B.

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9. APPENDICES

Appendix 1. Summary of Preclinical Investigations
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Appendix 1. Summary of Preclinical Investigations

SUMMARY OF PRECLINICAL INVESTIGATIONS

A comprehensive series of studies has been conducted to determine the therapeutic and toxicological potential of adefovir and adefovir dipivoxil. This section summarizes the principal findings of the preclinical studies and their relevance to the proposed human clinical use of adefovir dipivoxil.

1.1. Mechanism of Action

Adefovir, a nucleoside monophosphate analogue, is transported into cells and, through two phosphorylation reactions, is converted to adefovir diphosphate. Adefovir diphosphate functions as an inhibitor and chain-terminator of viral replication mediated by viral DNA polymerases and reverse transcriptases (RT). The viral DNA chain termination occurs because adefovir diphosphate can be incorporated in place of the natural substrate, deoxyadenosine triphosphate (dATP), and, since it lacks a 3' hydroxyl group, causes premature termination of DNA synthesis.

The kinetic inhibition constant (K_i) for adefovir diphosphate was 0.1 μM in an enzymatic assay using recombinant HBV polymerase, which is approximately 4-fold lower that the K_m for the competing substrate dATP.[39] Adefovir diphosphate selectively inhibits HBV DNA polymerases at concentrations 12-, 700-, and 10-fold lower than those needed to inhibit human DNA polymerases α, β, and γ, respectively (Table 1-1).[40] Adefovir diphosphate has an intracellular half-life of 12 to 36 hours in activated and resting lymphocytes.[41, 42]

Table 1-1. K_i Values of Adefovir Diphosphate, ddCTP, AZTTP, and K_m Values of dATP, dCTP, and dTTP Against Human DNA Polymerases

	K_i (μM)[1]			K_m (μM)[2]		
Enzyme	**ADV**	**ddCTP**	**AZTTP**	**dATP**	**dCTP**	**dTTP**
Human DNA Polymerase α	1.18	87	258	2.7	1.9	5.3
Human DNA Polymerase β	70.4	1.32	140	5.6	4.3	4.6
Human DNA Polymerase γ	0.97	0.034	18.3	0.72	0.5	0.54

1 The average relative standard error for K_i values is 16%.

2 K_m values are averages from at least three separate experiments. The average relative standard error for K_m values is 16%.

1.2. Preclinical Evaluation of Antiviral Activity

Anti-HBV Activity

The antihepadnaviral activity of adefovir has been demonstrated using *in vitro* assays and *in vivo* animal models, including duck and woodchuck hepatitis virus infections and HBV-infected transgenic mice.

Adefovir has demonstrated potent *in vitro* antiviral activity against HBV, duck HBV (DHBV), and woodchuck hepatitis virus (WHV) activity in primary hepatocytes and transformed hepatoblastoma cell lines.[43-47] In two hepatoma cell lines (HB611 and HepG2 2.2.15) permanently transfected with human HBV DNA, adefovir inhibited viral DNA synthesis with IC_{50} values in the range of 0.2 to 1.2 μM.

Adefovir has demonstrated additive or synergistic anti-DHBV activity in combination with lamivudine and penciclovir at several molar ratios in primary duck hepatocytes.[48] Adefovir was also previously reported to exert synergistic anti-HBV activity in combination with DAPD, emtricitabine, and L-FMAU at high molar ratios, but either additive or antagonistic anti-HBV activity at lower molar ratios with the same compounds in human hepatoblastoma cell lines.[49] Adefovir and tenofovir exerted additive activity against HBV in cell culture.[50] The clinical significance of these *in vitro* findings has not been established.

Drug-resistant mutations have been reported in chronic hepatitis B patients treated with lamivudine, famciclovir, and HBIg. In *in vitro* resistance studies, adefovir dipivoxil was active against all common forms of lamivudine-resistant HBV,[23, 26, 28] famciclovir-associated mutations,[51] and hepatitis B immunoglobulin escape mutations.[46]

In vivo animal studies demonstrated the activity and safety of adefovir in the duck model of DHBV replication, including activity in non-hepatocyte bile duct epithelial cells, and the activity and safety of adefovir dipivoxil in woodchuck and transgenic mouse models of WHV or HBV replication.

Woodchuck hepatitis virus is a hepadnavirus closely related to HBV and clinical progression of hepatitis due to chronic WHV infection in woodchucks closely parallels HBV infection in humans. In addition, treatment of woodchucks with FIAU revealed delayed hepatotoxicity at 12 weeks that was also observed in human studies but not in other animal toxicity studies.[52] To assess the antiviral activity and safety of adefovir dipivoxil, wild-caught or captive-bred adult woodchucks chronically infected with woodchuck hepatitis virus were given daily oral doses of 5 mg/kg or 15 mg/kg adefovir dipivoxil or placebo for 12 weeks.[53] These studies were therefore of adequate duration to assess the risk of hepatotoxicity. WHV DNA levels were reduced by a mean of 2.5 $\log_{10}$ copies/mL and 1.7 $\log_{10}$ copies/mL in the 15 and 5 mg/kg groups, respectively. WHV DNA levels returned to baseline after dosing was stopped. No adefovir-related changes in clinical signs, hematology, serum chemistry or body weight were noted. No histological differences were observed in the liver biopsies taken before treatment compared with those taken after treatment, except for a modest decrease in inflammation.

Antiretrovirus Activity

Adefovir is a potent and selective inhibitor of the *in vitro* replication of HIV-1, and related retroviruses including HIV-2, simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), and Moloney murine sarcoma virus (Mo-MSV).[54] Adefovir diphosphate inhibits HIV-1 RT, HCMV DNA polymerase and herpes simplex virus (HSV) DNA polymerase with K_I values of 0.012 µM,[54] 0.4 µM,[55] and 0.02 µM.[56] Adefovir has *in vitro* activity against herpesviruses, including HCMV, HHV-6, HHV-8, HSV-1, HSV-2, varicella zoster virus, and Epstein-Barr virus.[55, 57-61]

1.3. Cytotoxicity in Human Cells and Mechanisms of Toxicity

The concentrations of adefovir (80 to ~ 500 µM) required to induce *in vitro* cytotoxicity in the T lymphocyte derived MT-2 and CEM cells,[62-65] human hepatocyte derived HB611 and HepG2 2.2.15 cells,[43-45] and human renal proximal convoluted tubule cells,[66] were significantly higher than the concentration of adefovir (0.2 to 1.2 µM) required to exert anti-HBV activity in cell culture. Furthermore, the *in vitro* cytotoxic concentrations of adefovir are > 1,000 times greater than the maximum plasma concentrations (C_{max}, 0.064 µM) obtained in patients taking adefovir dipivoxil 10 mg daily (see Appendix 2).

Adefovir was evaluated in *in vitro* models of renal proximal tubular toxicity and compared with cidofovir and tenofovir to investigate the *in vivo* differences in nephrotoxicity observed between the three structurally related nucleotides.[66] Cidofovir exhibited the most pronounced inhibition of the growth of human renal proximal tubule epithelial cells (RPTECs), adefovir was less inhibitory and tenofovir did not show significant inhibition. When the antiviral potency of the three drugs was taken into account, the *in vitro* therapeutic index of adefovir was 7 to 8-fold higher than that of cidofovir and in a similar range as tenofovir; this appears to be in accordance with the safety profile of adefovir dipivoxil 10 mg daily for chronic hepatitis B.

Human renal organic anion transporter 1 (hOAT1), a protein localized in the basolateral membrane of the renal proximal tubule epithelium, has been implicated in the etiology of cidofovir and adefovir associated nephrotoxicity.[67] Transport kinetics experiments revealed a similar transport efficiency for cidofovir, adefovir, and tenofovir,[66] suggesting that interference with essential intracellular function(s) rather than a difference in renal transport is responsible for the differential nephrotoxicity profile of these compounds.

1.4. Mitochondrial Toxicity

Adefovir was characterized for its *in vitro* effects on mitochondrial DNA synthesis and compared with nucleoside analogs 3TC, FIAU, and ddC. Because the *in vivo* effects of nucleoside analogs appear to be most pronounced in liver and muscle tissues, the experiments were carried out in HepG2 human liver cells and in normal human skeletal muscle cells (SkMCs). No significant changes in mitochondrial DNA content were detected in human hepatoblastoma HepG2 cells and SkMCs following a treatment with 0.3 to 30 µM adefovir for 9 days. Similarly, mitochondrial DNA was unchanged in both cell types following treatment with 3TC. In contrast, 30 to 55% and > 90% reductions in mitochondrial DNA

were observed following incubation with 30 µM FIAU and ddC, respectively. [Report No. DDM-JPS-022593].

The *in vivo* effects of adefovir dipivoxil (40 mg/kg/day) were evaluated in a 4-week rat study focusing on cytochrome c oxidase and citrate synthase activities, mitochondrial DNA content in liver, kidney, and skeletal muscle, and plasma lactate concentrations as indicators of mitochondrial toxicity. No adverse effects were reported on any of the key parameters of mitochondrial function in this study. Additionally, there were no histological alterations associated with mitochondrial toxicity.[68]

1.5. Safety Pharmacology

Adefovir dipivoxil was evaluated in safety pharmacology studies for effects on general behavior in mice, renal, and gastrointestinal function in rats, and cardiovascular and respiratory function in dogs. Adefovir dipivoxil had no effect on general behavior in mice (Irwin test) at doses up to 100 mg/kg. In saline-loaded rats, a decrease in urine volume and electrolyte excretion (sodium, potassium, and/or chloride) occurred over 24 hours post-dose at 100 mg/kg. Decreased urine volume and potassium were observed over three hours in rats in the 30 mg/kg/day dose group. In the study of gastrointestinal transit of a charcoal meal in rats, excess fluid was observed in the stomach and intestines at doses ≥ 30 mg/kg; there was no effect on gastrointestinal transit in any dose group. No adefovir dipivoxil-related effects on cardiovascular and respiratory function were observed in anesthetized dogs following administration of a single intraduodenal dose of adefovir dipivoxil up to 12 mg/kg.

1.6. Absorption, Distribution, Metabolism and Excretion

Following oral administration of adefovir dipivoxil in mice, rats and monkeys maximum adefovir plasma concentrations were reached within 0.5 to 1.5 hour and declined in a biphasic manner; observed terminal half-life values were approximately 6, 6, and 4 hours, respectively. The oral bioavailability of adefovir dipivoxil was greatest in rats (34% to 47%) and least in monkeys (21-35%). Dose proportional pharmacokinetics of adefovir were observed following oral administration of adefovir dipivoxil. In general, repeat dose studies demonstrated similar pharmacokinetic parameters to single dose studies.

Adefovir dipivoxil is metabolized via nonspecific esterases to adefovir via the monoester (mono-POM-PMEA). The prodrug moiety was efficiently cleaved in all species. Consistent with the lack of metabolism of adefovir in intestinal and liver preparations, no circulating metabolites of adefovir were detected.

Adefovir did not inhibit the catalytic activity of the human cytochrome P450s examined at concentrations up to 300 µM. However, cytochrome P450 3A4 was inhibited by adefovir dipivoxil at a concentration of 19 and 83 µM using midazolam and testosterone as substrates. Further analysis for the K_i of inhibition of cytochrome P450 3A4 by adefovir dipivoxil demonstrated values of 8.8 and 41 µM. This inhibition was considered to be negligible since adefovir dipivoxil is rapidly degraded to adefovir and that the overall concentration of adefovir dipivoxil would not approach the inhibitory concentrations or K_i concentrations in humans.

Following oral administration of adefovir dipivoxil, extensive tissue distribution of adefovir was observed in all species with the gastrointestinal tissues, liver and kidney as the major sites of distribution in rats and monkeys. Following intravenous administration, adefovir was excreted unchanged in the urine of all animal species tested and renal excretion was identified as the primary route of elimination.

1.7. Toxicology

The definitive preclinical toxicology studies in which adefovir dipivoxil was administered orally were conducted in mice, rats and cynomolgus monkeys. The target organs of toxicity identified in the toxicology program were kidney, gastrointestinal tract, liver and hemopoietic system.

1.7.1. Subacute and Chronic Toxicity

Subacute and chronic toxicology studies in mice, rats, and monkeys identified the kidney, liver, gastrointestinal, and hemopoietic system as potential target organs for adefovir-related toxicities.

Kidney:
Adefovir-related nephrotoxicity was characterized by renal tubular nephropathy (variably described as karyomegaly, cytomegaly, tubular dilatation, degeneration/regeneration, individual tubular epithelial cell necrosis, or elevations in BUN and/or creatinine) in all species evaluated.

The incidence and severity of renal tubular nephropathy were related to dose and duration of treatment. In mice administered adefovir dipivoxil 1 mg/kg/day chronically (2-year study), renal tubular epithelial karyomegaly was the only effect observed; this is considered the no-adverse effect level (NOAEL) based on the considerations detailed above. Kidney changes considered to be of pathologic consequence were seen in mice at 3 mg/kg/day (minimum effect level [MEL]; systemic exposure approximately 3 times human).[69] In rats, a NOEL of 2-4 mg/kg/day was observed in the 2-, 4-, and 26-week studies. In the 2-year rat study, renal tubular karyomegaly was the only effect observed in kidneys at doses of 0.5 to 5 mg/kg/day. Kidney toxicity was observed in rats at doses ≥ 12 mg/kg/day (MEL; systemic exposure 10 times human) in the 2- and 4-week studies.[70-72] The NOEL in monkeys in the 13- and 52-week studies was 1 mg/kg/day. Renal tubular karyomegaly with occasional individual tubular cell necrosis was observed in monkeys at doses ≥ 5 mg/kg/day (MEL; systemic exposure approximately 3 times human) in the 13-week study.[73, 74] Additional kidney changes were observed at 25 mg/kg/day in the 4- and 13-week studies.

In summary, nephrotoxicity was observed in animal models at doses producing systemic exposures approximately 3 to 10 times that achieved in humans at the recommended therapeutic dose of 10 mg/day.

Liver:
Adefovir-related histological changes in liver were evaluated in 2 species and were only seen in mice. Dose-related changes in mice at doses ≥ 10 mg/kg/day in the 13-week study

included hepatocellular karyo/cytomegaly, single cell necrosis and oval cell and focal hepatocellular hyperplasia. In the 2-year mouse study that evaluated lower doses (1, 3, and 10 mg/kg/day), there was no evidence of hepatocellular toxicity suggesting that the 10 mg/kg/day dose level (approximately 10 times the human exposure) is a threshold for liver effects in this species. In monkey studies of adefovir dipivoxil, elevations in liver transaminases were observed but not accompanied by histological evidence of hepatic injury or inflammation. At doses of 5 to 25 mg/kg/day (systemic exposure approximately 3 to 27 times human), elevations in ALT and/or AST were modest (< 3-fold) and reversible upon discontinuation of treatment. These data, considered in conjunction with the clinical safety data, suggest little potential for adverse effect on the liver in humans receiving adefovir dipivoxil at the recommended dose of 10 mg/day.

Gastrointestinal Tract:
Dose-related hyperplastic, degenerative, and inflammatory changes in the gastrointestinal tract were observed in rats (≥ 37 mg/kg/day, 2 weeks) and monkeys (≥ 8 mg/kg/day, 4 weeks) administered high doses in short-term studies. Gastrointestinal toxicity was absent in monkeys following 13 weeks of adefovir dipivoxil at doses comparable to or greater than those associated with gastrointestinal toxicity in the 4 week study. The gastrointestinal toxicity appears to be largely due to local irritation; however, as enteropathy of the intestines was observed following subcutaneous administration of high doses of adefovir in monkeys (20 mg/kg/day, 4-week study), a systemic component may not be ruled out. Based on considerations of dose and local concentration in the gastrointestinal tract, there is little concern for adverse effects in the gastrointestinal tract in patients receiving adefovir dipivoxil at the recommended therapeutic dose.

Hematopoietic Systems:
Adefovir dipivoxil-related toxicity to the hematopoietic system (including bone marrow) was observed in the 13-week study in mice at doses of 10-100 mg/kg/day (systemic exposures 11 to 76 times human). Findings included lymphoid necrosis/atrophy of the spleen and thymus, slight erythroid hypocellularity of the bone marrow, slight spleen extramedullary hematopoiesis, decreased thymus and spleen weights and decreased erythrocyte parameters.

Studies of adefovir administered by intravenous or subcutaneous injection allowed evaluation of systemic exposures higher than were achieved following oral administration of adefovir dipivoxil. In 4-week studies of adefovir administered subcutaneously lymphoid depletion of spleen, thymus and/or lymph nodes, hypocellularity in the bone marrow were observed in rats (≥ 20 mg/kg/day) and monkeys (≥ 20 mg/kg/day; approximately > 250 times the human exposure). This high dose/exposure toxicity to rapidly proliferating cells is not unexpected for a nucleotide analog. Given the large margin of safety in animals, and lack of adverse effects in clinical studies of adefovir dipivoxil at doses as high as 120 mg/day, the potential for adverse effects on the hematopoietic system at the recommended therapeutic dose is minimal.

1.7.2. Reproductive Toxicology

No embryotoxic or teratogenic effects were observed in rats at doses up to 35 mg/kg. The maternal and fetal no-observable-adverse-effect-level (NOAEL) for rats was 10 mg/kg/day.

No embryotoxic or teratogenic effects were observed in rabbits administered adefovir dipivoxil at oral doses up to 20 mg/kg/day. In a study of fertility and early embryonic development to implantation, no effects were observed on male and female fertility or reproductive performance in rats administered adefovir dipivoxil at oral doses up to 30 mg/kg/day. Investigation of effects on pre- and postnatal development, including maternal function in rats, indicated developmental toxicity (increased pup deaths and decreased birth weights) and maternal toxicity (decreased body weights and food consumption) only at a 40 mg/kg/day oral dose of adefovir dipivoxil.

The administration of adefovir intravenously in pregnant rats resulted in embryotoxicity, increased incidence of fetal malformations and common variations, but only at maternally toxic doses.

While the data from the embryo-fetal development study of adefovir dipivoxil administered orally is most relevant for human risk assessment, the findings with intravenous adefovir should be taken into consideration. There are no studies in human pregnancy and animal data may not always be predictive of human response. Therefore, adefovir dipivoxil should be used during pregnancy only if clearly needed and after careful consideration of risks and benefits.

1.7.3. Genetic Toxicology and Carcinogenicity

The profile of adefovir and adefovir dipivoxil in genetic toxicity and carcinogenicity tests is similar to other nucleoside analogs in that it appears to induce chromosomal aberrations (but not point mutations) in *in vitro* studies[75] but is not genotoxic or carcinogenic in *in vivo* models. Specifically, like lamivudine, adefovir was negative in the *in vitro* bacterial mutation assay[75] and positive in the chromosome aberration assay in human peripheral blood lymphocytes; adefovir dipivoxil was positive in the mouse lymphoma assay.[76] Adefovir dipivoxil was negative in the *in vivo* mouse micronucleus assay. There was no evidence of carcinogenicity following two years of daily oral administration of adefovir dipivoxil at the predicted maximum tolerated dose (MTD) in the mouse (10 mg/kg/day; systemic exposure approximately 10 times human)[77] or the rat (5 mg/kg/day; systemic exposure approximately 4-5 times human).[76] On the basis of these studies, it is concluded that the genetic toxicity and carcinogenic potential of adefovir dipivoxil present no concern for carcinogenicity at the intended clinical dose.

1.7.4. Toxicity of Hydrolysis Products

Pivalic Acid:
Pivalic acid, a product of the *in vivo* metabolism of adefovir dipivoxil to adefovir, conjugates with serum free carnitine and is renally excreted. In monkey studies, serum free and total serum carnitine levels were reduced in a manner dependent on dose and duration of treatment. No apparent toxicity (clinical or histological) attributable to carnitine reduction was evident in the monkeys. No adverse effects attributable to carnitine depletion have been reported in clinical studies among patients receiving adefovir dipivoxil 10 mg.

Formaldehyde:
During the hydrolysis of the pivaloyloxymethyl promoiety formaldehyde is released. Formaldehyde is not a reproductive toxicant in mice or dogs. However, formaldehyde is genotoxic in a number of *in vitro* tests and causes increased incidence of nasal tumors following chronic inhalational administration to rats.[75] Formaldehyde was not carcinogenic when administered to rats.[78] The estimated daily exposure to formaldehyde associated with therapeutic doses of adefovir dipivoxil is > 10 fold less than the EPA's estimated daily lifetime exposure considered to be without any appreciable deleterious effects in humans.[75] On the basis of available safety data in animal models, adverse reactions associated with formaldehyde ingestion in patients receiving therapeutic doses of adefovir dipivoxil are not anticipated.

1.8. Conclusions of Preclinical Evaluation

The key findings of the pharmacology, virology, ADME, and toxicology evaluation of adefovir dipivoxil are:

- Adefovir has potent anti-HBV activity *in vitro* and *in vivo* against wild-type and drug-resistant mutant of hepatitis B virus.

- There was no evidence for adefovir-related mitochondrial toxicity from *in vitro* or *in vivo* studies.

- Renal toxicity was the major target organ toxicity identified in all three species evaluated. The renal effects occur in a predictable, dose-related manner and predict the dose-limiting toxicity in humans.

- Gastrointestinal toxicity in animals appears to be associated with high dose local intestinal exposure and should not pose a safety concern in humans at the recommended therapeutic dose.

- Toxic effects on the hematopoietic system occurred only at relatively high doses of adefovir administered parenterally and have a large margin of safety relative to the human clinical dose.

- There were no adverse reproductive effects in male or female animals and no fetal developmental/teratogenic effects identified in rats or rabbits treated with adefovir dipivoxil. When administered at maternally toxic doses, intravenous adefovir was teratogenic. Since there are no studies in pregnant women, adefovir should be used in pregnancy only if clearly needed, and after careful consideration of risks and benefits.

- Adefovir dipivoxil was not carcinogenic in chronic rat and mouse studies.

Appendix 2. Summary of Clinical Pharmacology

SUMMARY OF CLINICAL PHARMACOLOGY

This appendix summarizes the human pharmacokinetics of adefovir following oral administration of adefovir dipivoxil 10 mg once daily, the proposed therapeutic dose for the treatment of chronic hepatitis B in adults.

The pharmacokinetics of adefovir have been examined in patients with chronic hepatitis B (GS-00-472, study 472) and in two special populations, renally impaired (GS-00-473, study 473) and hepatically impaired (GS-00-474, study 474) non HBV-infected subjects. Pharmacokinetic data are also described from two studies in healthy volunteers, a steady state drug-drug interaction study (GS-00-475, study 475) and a food effect study (GS-00-476, study 476). These pharmacokinetic studies are summarized in Table 2-1.

In addition, supportive in vitro, clinical pharmacokinetic, and safety data from studies of higher doses of intravenous adefovir and oral adefovir dipivoxil doses 6 to greater than 12-fold the proposed 10 mg dose are summarized to provide information regarding absolute oral bioavailability, dose-proportionality and drug-drug interaction potential.

Table 2-1. Summary of Adefovir Dipivoxil Clinical Pharmacokinetic Studies

Study No.	Study Population	Enrolled	Location	Status (as of June 2002)
472 Single and Multiple Dose PK Study	Patients with chronic hepatitis B infection	14	US, France	PK evaluations complete
473 Renal Impairment Study	Non HBV-infected subjects +/- hepatic impairment	41	France	Complete
474 Hepatic Impairment Study	Non HBV-infected subjects +/- hepatic impairment	24	France	Complete
475 Steady State Drug Interaction Study	Healthy subjects	81	US	Complete
476 Food Effect Study	Healthy subjects	18	US	Complete

2.1. Pharmacokinetics in Chronic Hepatitis B Patients and Healthy Subjects

In patients with chronic hepatitis B and healthy subjects, single and multiple oral administrations of adefovir dipivoxil 10 mg resulted in a reproducible adefovir concentration time profile and dose-proportional pharmacokinetics (Figure 2-1, Table 2-2). Following oral dosing, maximum observed adefovir concentrations (C_{max}) in plasma were rapidly achieved

(0.76 to 1.75 hours, median values) and then declined with a well characterized median (terminal) elimination half-life of 6 to 7 hours. The active antiviral intracellular anabolite, adefovir diphosphate also exhibits a prolonged intracellular half-life (12 to 36 hours), allowing for once daily dosing of adefovir dipivoxil 10 mg.

The absolute oral bioavailability of adefovir from a 10 mg tablet of adefovir dipivoxil is approximately 59% (median value), and the systemic adefovir exposure was unaffected by administration with a (high fat) meal. The steady state urinary recovery (A_e) of adefovir was approximately 45.3% (median value) of an administered dose. Adefovir renal clearance (CL_{renal}) was approximately twice glomerular filtration rate (calculated creatinine clearance (CL_{cr}), Cockroft-Gault method), indicating contribution of tubular secretion to the excretion of adefovir. The steady state pharmacokinetics of adefovir were similar to those following a single dose, without accumulation of drug following 7 days of once daily dosing of adefovir dipivoxil 10 mg. Primary pharmacokinetic data following single and multiple doses in patients with chronic hepatitis B infection are presented in Table 2-3.

Figure 2-1. Single Dose Adefovir Concentration-Time Profiles (mean ± 95% CI) following Oral Administration of Adefovir Dipivoxil 10 or 60 mg to Patients with Chronic Hepatitis B and Healthy Subjects

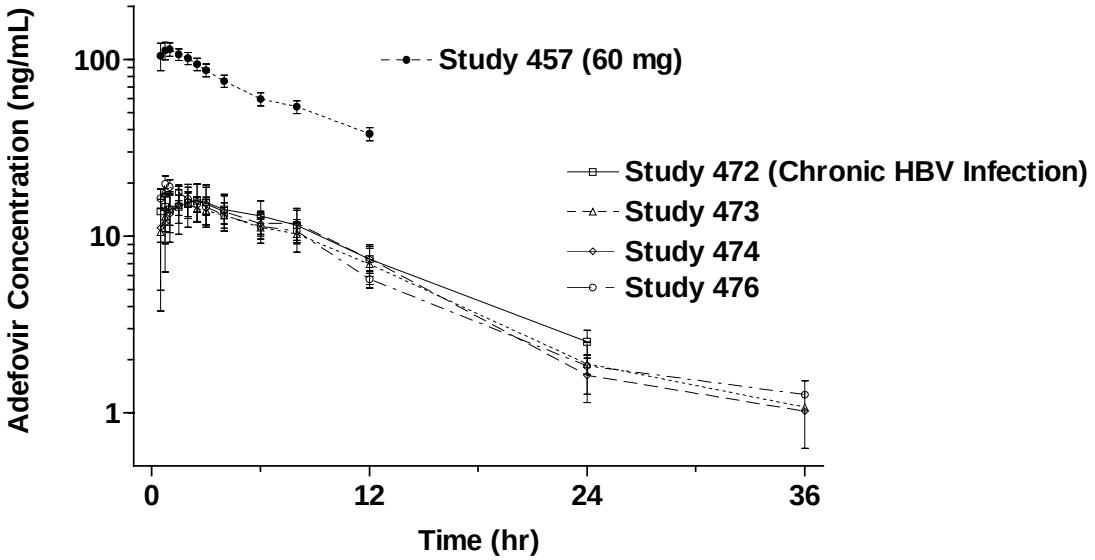


Table 2-2. Pharmacokinetics of Adefovir Following Single Oral Doses of Adefovir Dipivoxil 10 or 60 mg in Patients with Chronic Hepatitis B and Healthy Subjects

Pharmacokinetic Parameter	**ADV 10 mg**				**ADV 60 mg**
Study	**472[c]**	**473[a]**	**474[a]**	**476**	**457**
N	14	7	8	17	37
Mean $AUC_{0-\infty}$ (ng/hr/mL) Range	210 110 - 356	197 145 - 264	198 157 - 292	192 128 - 248	1160 715 - 1790
Mean C_{max} (ng/mL) Range	17.5 9.66 – 30.6	17.5 13.3 – 21.8	18.3 13.5 – 26.4	20.4 13.4 – 27.8	125 71.2 - 178
Median T_{max} (hr) Range	1.75 0.58 – 4.00	1.00 0.50 – 3.00	1.25 0.50 – 2.50	0.76 0.49 2.00	0.79 0.50 – 3.02
Median $T_{½\lambda z}$ (hr) Range	7.22 4.72 – 10.7	7.01 5.44 – 8.94	6.17 5.44 – 7.07	6.42 4.30 – 7.64	8.08 4.80 – 26.3[b]
Median CL_{renal} (mL/min) Range	206 87.9 - 400	211 172 - 316	-	-	-

a Unimpaired healthy subject cohorts from renal and hepatic impairment studies

b Outlier value, second highest value = 10.7 hours

c Chronic hepatitis B patients

Table 2-3. Pharmacokinetics of Adefovir Following Single and Multiple Oral Doses of Adefovir Dipivoxil 10 mg in Patients with Chronic Hepatitis B: Study 472

	ADV 10 mg	
Pharmacokinetic Parameter	**Day 1-2**	**Day 7**
N	14	14
Mean AUC (ng/hr/mL)[a] Range	210 110 - 356	204 124 - 367
Mean C_{max} (ng/mL) Range	17.5 9.66 – 30.6	18.3 9.19 – 38.7
Median T_{max} (hr) Range	1.75 0.58 – 4.00	1.00 0.50 – 6.00
Median $T_{½\lambda z}$ (hr) Range	7.22 4.72 – 10.7	7.14 4.22 – 17.4
Median CL_{renal} (mL/min) Range	206 87.9 - 400	216 84.1 - 340

a $AUC_{0-\infty}$ for day 1-2 and $AUC_{0-\tau}$ for day 7.

2.2. Pharmacokinetics in Special Patient Populations

Renal Impairment

Study 473 demonstrated reduced adefovir elimination and higher systemic drug exposure in subjects with moderate and severe renal impairment (CL_{cr} < 50 mL/min) (Table 2-3). Consistent with renal elimination, adefovir concentrations in plasma plateaued at high levels in patients with end stage renal disease (ESRD) requiring hemodialysis. Hemodialysis efficiently removed adefovir with approximately 36% of a dose eliminated over a 4-hour hemodialysis session.

Table 2-4. Pharmacokinetics Parameters of Adefovir Dipivoxil in Subjects with Varying Degrees of Renal Function and ESRD: Study 473

Pharmacokinetic Parameter	Renal Function Impairment Creatinine Clearance (mL/min)			ESRD	
	Mild (50-79)	Moderate (30-49)	Severe (10-29)	Intra-Dialysis	Inter-Dialysis
N	8	7	10	8	8
Mean C_{max} (ng/mL) Range	22. 1 15.8 – 28.2	27.3 15.9 – 38.5	50.7 34.7 – 72.8	59.9 44.2 – 87.1	81.9 54.4 - 150
Mean $AUC_{0-\infty}$ (ng•hr/mL) Range	261 174 – 340	420 214 – 691	1120 420 – 2760	2170[1] 1560 -3110	2100[2] 1410 - 3560
Median CL_{renal} (mL/min) Range	149 94.7 - 205	85.9 49.5 – 119	34.8 11.6 – 75.8	-	-
Median A_e (% of dose) Range	43.7 27.9 – 50.5	38.6 27.7 – 42.7	35.4 31.9 – 66.2	-	-

1 AUC_{0-48}

2 AUC_{0-30}

Since primary renal impairment or hepatorenal syndrome are common extrahepatic sequelae of chronic hepatitis B disease, dose interval adjustments are recommended for patients with creatinine clearance of < 50 mL/min or those with ESRD requiring hemodialysis (Table 2-5).

Table 2-5. Recommendations for Dose Interval Modification of Adefovir Dipivoxil in Renal Impairment

Creatinine Clearance (mL/min)					Requiring Hemodialysis
> 80	50–80	20–49	10–19	< 10	
Normal Dosage Regimen i.e., 10 mg every 24 hours		10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days	10 mg every 7 days post hemodialysis

Through use of pharmacokinetic modeling and simulations of steady state systemic adefovir exposure, these recommended dose interval adjustments are predicted to reduce drug accumulation and target trough concentrations observed in healthy subjects and HBV-infected patients with normal renal function. In patients with ESRD, a dosing regimen of once-weekly, following completion of hemodialysis is recommended to allow for dialysis removal of the majority of each adefovir dose while also maintaining therapeutic systemic adefovir exposures. No pharmacokinetic data are available at this time in patients undergoing other forms of dialysis.

These recommended renal dosing guidelines are being evaluated in a pharmacokinetic, efficacy, and safety study of adefovir dipivoxil 10 mg in chronic hepatitis B patients with lamivudine-resistant hepatitis B with varying degrees of renal impairment. Also, a liquid formulation (suspension) is currently under development. Once available, revised dosing guidelines for once daily dosing of lower doses of adefovir dipivoxil will be developed.

Hepatic Impairment

Study 474 demonstrated no substantial alterations in the pharmacokinetics of adefovir in subjects with moderate or severe hepatic impairment (Child-Pugh-Turcotte classifications B and C, respectively) relative to the pharmacokinetics in unimpaired subjects. No dosing modifications are recommended in patients with hepatic impairment.

Demographic Effects

There were no substantial differences observed in the steady state pharmacokinetics of adefovir with regard to demographic variables including age, body weight, sex, or race (studies 472 and 475). However, there are no pharmacokinetic data available in the elderly at this time. Studies in pediatric populations, including a dose-ranging pharmacokinetic evaluation are currently in development.

2.3. Interactions

In vitro and clinical pharmacokinetic data indicate that adefovir is not a substrate or inhibitor of human cytochrome P450 enzymes responsible for the biotransformation of the majority of drugs. The in vitro protein binding of adefovir to human plasma or serum proteins is low (≤ 4%), indicating that adefovir is unlikely be involved in drug-drug or drug-disease protein binding-displacement interactions in vivo. A preclinical study of adefovir pharmacokinetics in p-glycoprotein deficient mice does not indicate effects of this drug transporter on adefovir systemic exposure. These data suggest a low potential for clinically relevant drug-drug interactions with adefovir dipivoxil 10 mg based on these most frequently encountered mechanisms.

Study 475 was a steady state clinical pharmacokinetic drug-drug interaction study conducted with frequently administered medications in the chronic hepatitis B patient population (lamivudine, ibuprofen, acetaminophen, or trimethoprim/sulfamethoxazole). This study did not identify clinically relevant pharmacokinetic drug-drug interactions between adefovir dipivoxil 10 mg and these agents, including those that share a component of active tubular secretion by the kidney. The pharmacokinetics of each drug when co-administered with adefovir dipivoxil 10 mg were equivalent to those following their administration alone. Similarly, there were no alterations in the pharmacokinetics of adefovir when adefovir dipivoxil 10 mg was dosed with lamivudine, acetaminophen, or trimethoprim/sulfamethoxazole. Small increases in adefovir C_{max} and $AUC_{0-\tau}$ of approximately 33% and 23%, respectively, were identified when adefovir dipivoxil 10 mg was coadministered with high doses (800 mg TID) of ibuprofen. A concurrent increase in steady state adefovir urinary recovery (22%) without alterations in renal clearance were also observed, suggesting increased adefovir relative oral bioavailability by a mechanism that is

not understood. Given the small magnitude of this alteration at the maximum recommended dose of ibuprofen, dose adjustment of adefovir dipivoxil 10 mg is not recommended.

Drug interactions between adefovir dipivoxil and cyclosporine and tacrolimus have not been evaluated in patients post-liver transplantation. Both of these immunosuppressant agents are principally metabolized in the liver and therefore there is limited reason to expect potential drug interactions with adefovir dipivoxil. However, both cyclosporine and tacrolimus are known nephrotoxic agents; the elimination of adefovir may be affected in patients who experience these untoward effects of chronic immunosuppressant therapy. Gilead Sciences is planning to collect and analyze immunosuppressant pharmacokinetic and dosing data in addition to concomitant medication information from liver transplantation patients participating in study 435 to ascertain the need for additional *in vitro* and/or clinical studies of the drug-drug interaction potential between adefovir dipivoxil and these agents.

In the HIV program, adefovir dipivoxil was dosed in combination with antiretrovirals including zidovudine, saquinavir, nelfinavir, nevirapine, indinavir, efavirenz, delavirdine, didanosine and/or lamivudine at doses 6 to greater than 12-fold greater than the 10 mg dose proposed for the treatment of chronic hepatitis B infection. In general, clinical experience and pharmacokinetic data from this program did not indicate clinically relevant drug-drug interactions in the HIV-infected population.

In a dedicated pharmacokinetic drug-drug interaction study that studied adefovir dipivoxil 60 mg and six antiretroviral drugs (study GS-99-430), didanosine systemic exposure (AUC) was increased (29%) when co-administered with adefovir dipivoxil. This increase may be the result of an increase in the relative oral bioavailability of didanosine, which has been observed with other purine analogue antiviral compounds. Analyses of clinical adverse events in placebo controlled trials within the HIV safety database showed no increased risk of didanosine-related adverse events (pancreatitis, etc.) when didanosine was given concomitantly with adefovir dipivoxil at doses of 60 mg or 120 mg daily.

Another study (study GS-97-414, ACTG 359), evaluated adefovir dipivoxil 120 mg in HIV-infected patients with or without delavirdine in double protease inhibitor regimens containing saquinavir in combination with either ritonavir or nelfinavir. In a pharmacokinetic sub-study (ACTG 884), data reported by the AIDS Clinical Trials Group suggested no effect of adefovir dipivoxil 120 mg on the exposures of ritonavir or nelfinavir but possible decreases in serum concentrations of delavirdine and saquinavir. Interpretation of the results of this study is difficult in light of the complex CYP450 interactions between delavirdine and HIV protease inhibitors.

2.4. Conclusions of Clinical Pharmacokinetic Studies

Following oral administration of adefovir dipivoxil 10 mg, the pharmacokinetics of adefovir are predictable and consistent across all populations investigated. Adefovir dipivoxil 10 mg may be taken without regard to meals as the oral bioavailability of adefovir is unaffected by food. Adefovir is eliminated as unchanged drug by the kidney via a combination of tubular secretion and glomerular filtration. Clinical safety and pharmacokinetic data indicate a limited potential for drug interactions between adefovir dipivoxil 10 mg and drugs used in the

chronic hepatitis B patient population. A dose interval adjustment to one 10 mg tablet once every 48 and once every 72 hours is recommended in patients with moderate and severe renal impairment, respectively. In patients with ESRD and/or in hemodialysis (CLcr < 10 mL/min) adefovir dipivoxil should be dosed once weekly following hemodialysis. No dosing modifications are required in patients with hepatic impairment.

Appendix 3. Results of Study 437 Incorporating Adefovir Dipivoxil 30 mg Dose Group

RESULTS OF PRIMARY AND SECONDARY EFFICACY ANALYSES

3.1. Effects on Liver Histology (0-48 Weeks)

In study 437, the primary efficacy endpoint was histological improvement at week 48 in which missing or unassessable 48 week biopsies were treated as failures. A significantly higher proportion of patients had histologic improvement (defined as ≥ 2 point decrease in the Knodell necroinflammatory score with no concurrent worsening in the Knodell fibrosis score) at week 48 in both adefovir dipivoxil dose groups compared with the placebo group ($p < 0.001$). The primary evaluation defined for the study was the comparison of adefovir dipivoxil 10 mg to placebo. The comparison of adefovir dipivoxil 30 mg to placebo was considered a secondary endpoint. Statistically significant histologic improvement was also demonstrated in the analysis where missing or unassessable 48 week biopsies were excluded. Results are presented in Table 3-1.

Table 3-1. Patients With Histologic Improvement at Week 48 (ITT): Study 437

	Placebo (N = 167)	ADV 10 mg (N = 171)	ADV 30 mg (N = 173)
ITT (missing/unassessable week 48 biopsies=failure)			
n (with baseline biopsy)	161	168	165
Improvement[1], n (%)	41 (25%)	89 (53%)	98 (59%)
No improvement, n (%)	105 (65%)	61 (36%)	47 (28%)
Missing data, n (%)	14 (9%)	16 (10%)	16 (10%)
Unassessable data, n (%)	1 (<1%)	2 (1%)	4 4 (2%)
Treatment difference, % (95% CI) [2]		27.5% (17.4%, 37.6%)	33.9% (23.9%, 44.0%)
p-value[3]		<0.001	<0.001
ITT(missing/unassessable week 48 biopsies excluded)			
n (with baseline and wk 48 biopsies)	146	150	145
Improvement[1], n (%)	41 (28%)	89 (59%)	98 (68%)
No improvement, n (%)	105 (72%)	61 (41%)	47 (32%)
Treatment difference, % (95% CI) [2]		31.3% (20.5%, 42.0%)	39.5% (29.0%, 50.0%)
p-value[3]		< 0.001	< 0.001

1 Improvement defined as ≥ 2 point decrease in the Knodell necroinflammatory score from baseline at week 48 with no concurrent worsening in the Knodell fibrosis score.

2 Treatment difference and 95% confidence interval for the difference in the proportion of patients with improvement (relative to placebo).

3 From general association Cochran-Mantel-Haenszel statistic.

The significant improvement in liver histology in the adefovir dipivoxil treatment groups (10 mg, 30 mg) was also demonstrated by significant changes from baseline in the total Knodell HAI score and the necroinflammatory portion of the Knodell score after 48 weeks when compared with placebo (Table 3-2). For fibrosis scores, there was a trend towards improvement seen in the adefovir dipivoxil 10 mg group ($p = 0.06$), and a statistically significant improvement in the adefovir dipivoxil 30 mg group when compared with the placebo group ($p = 0.001$).

Table 3-2. Changes in Knodell HAI Score from Baseline at Week 48 (ITT Population with Assessable Biopsies at Baseline and Week 48): Study 437

	Placebo (N = 146)	**ADV 10 mg (N = 150)**	**ADV 30 mg (N = 145)**
Total Knodell HAI			
Mean ± SD	-0.17 ± 3.51	-2.76 ± 3.60	-3.48 ± 3.66
Median	0	-3	-4
Q1, Q3	-2, 2	-5, 0	-6, 0
p-value[1]	-	< 0.001	< 0.001
Necroinflammatory			
Mean ± SD	-0.16 ± 3.06	-2.58 ± 3.22	-3.17 ± 3.30
Median	0	-2	-3
Q1, Q3	-2, 1	-5, 0	-5, 0
p-value[1]	-	< 0.001	< 0.001
Fibrosis			
Mean ± SD	-0.01 ± 0.86	-0.18 ± 0.84	-0.32 ± 0.80
Median	0	0	0
Q1, Q3	0, 0	0, 0	0, 0
p-value[1]	-	0.061	0.001

1 Wilcoxon Rank Sum Test

Similarly, the results of the blinded ranked assessment of baseline and week 48 biopsies, demonstrated that patients treated with adefovir dipivoxil 10 mg had improved necroinflammatory ($p < 0.001$) and fibrosis ($p < 0.001$) scores relative to placebo-treated patients. Similar statistically significant improvements in the necroinflammatory and fibrosis assessments were also seen in the adefovir dipivoxil 30 mg dose group (Table 3-3).

Table 3-3. Ranked Assessment of Necroinflammatory and Fibrosis Scores—ITT Population

	Placebo N = 167	ADV 10 mg N = 171	ADV 30 mg N = 173
Assessable Baseline and Week 48 Biopsies Available	145	150 (88%)	145
Necroinflammatory			
Improved	59 (41%)	107 (71%)	112 (77%)
Same	37 (26%)	23 (15%)	18 (12%)
Worse	49 (34%)	20 (13%)	15 (10%)
p-value*		< 0.001	< 0.001
Fibrosis			
Improved	35 (24%)	62 (41%)	78 (54%)
Same	72 (50%)	67 (45%)	53 (37%)
Worse	38 (26%)	21 (14%)	14 (10%)
p-value*		< 0.001	< 0.001

* From Cochran-Mantel-Haenszel statistic.

3.2. Effects on HBV DNA (0-48 Weeks)

The antiviral activity of adefovir dipivoxil (10 mg, 30 mg) was demonstrated by the statistically significant decreases in serum HBV DNA levels at week 48 seen in both active treatment groups (Table 3-4). The median time-weighted average change from baseline in serum HBV DNA up to week 48 ($DAVG_{48}$) was -2.84 $\log_{10}$ copies/mL in the adefovir dipivoxil 10 mg group, -4.10 $\log_{10}$ copies/mL in the adefovir dipivoxil 30 mg group compared with -0.43 $\log_{10}$ copies/mL in the placebo group ($p < 0.001$).

As displayed graphically in Figure 3-1, there was a rapid decrease in the median serum HBV DNA $\log_{10}$ change from baseline in patients treated with adefovir dipivoxil 10 mg with statistically significant differences compared with placebo evident from week 4 onwards. At week 48, the median change from baseline in serum HBV DNA was -3.52 $\log_{10}$ copies/mL in the adefovir dipivoxil 10 mg group, -4.76 $\log_{10}$ copies/mL in the adefovir dipivoxil 30 mg treatment group and -0.55 $\log_{10}$ copies/mL in the placebo group. Significantly more patients in both the adefovir dipivoxil 10 mg and 30 mg groups had serum HBV DNA levels below 400 copies/mL (the lower limit of quantification for the Roche Amplicor assay) at week 48 compared with patients in the placebo (Table 3-4).

Figure 3-1. Median and Interquartile Range of Change in HBV DNA (Log_{10}) from Baseline to Week 48 (ITT): Study 437

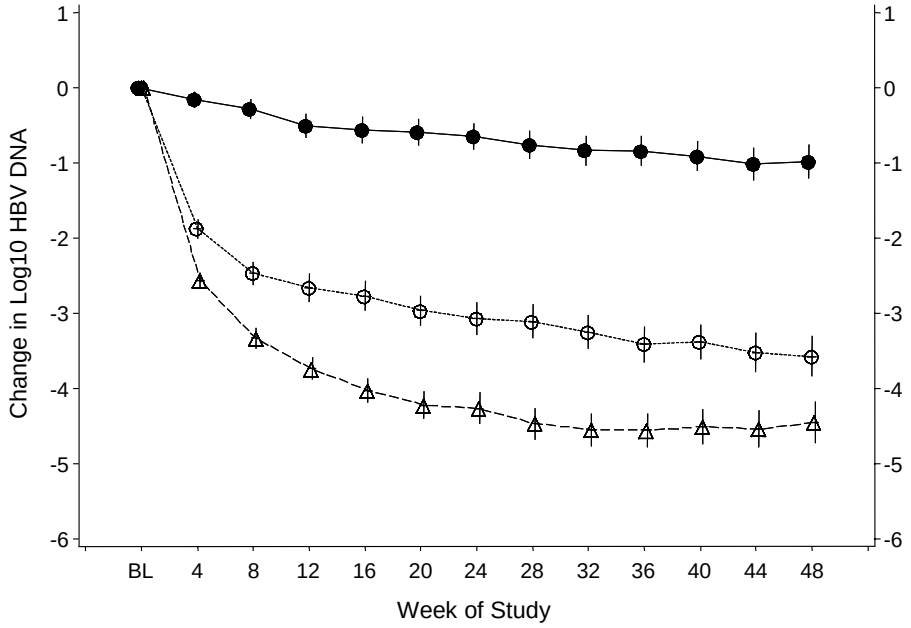


Table 3-4. Change in Serum HBV DNA (log_{10} copies/mL) at Week 48

	Placebo N = 167	**ADV 10 mg N = 171**	**ADV 30 mg N = 173**
Serum HBV DNA			
< 400 copies/mL	0 (0%)	36 (21%)	67 (39%)
95% CI		14.9% to 27.2%	31.5% to 46.0%
p-value		< 0.001	< 0.001
≥ 400 copies/mL	148 (89%)	116 (68%)	79 (46%)
Missing data[a]	19 (11%)	19 (11%)	27 (16%)
N	167	171	173
$DAVG_{48}$[b]			
Mean ± SD	-0.68 ± -0.88	-2.98 ± -1.22	-4.05 ± 1.14
p-value		< 0.001	< 0.001
Median	-0.43	-2.84	-4.10
Q1 to Q3	-0.97 to –0.15	-3.86 to –2.04	-4.82 to –3.54
N	167	170	171
Change at Week 48			
Mean ± SD	-0.98 ± 1.32	-3.57 ± 1.64	-4.45 ± 1.62
Median	-0.55	-3.52	-4.76
Q1 to Q3	-1.62 to –0.20	-4.91 to –2.22	-5.54 to 3.91
N	148	152	146

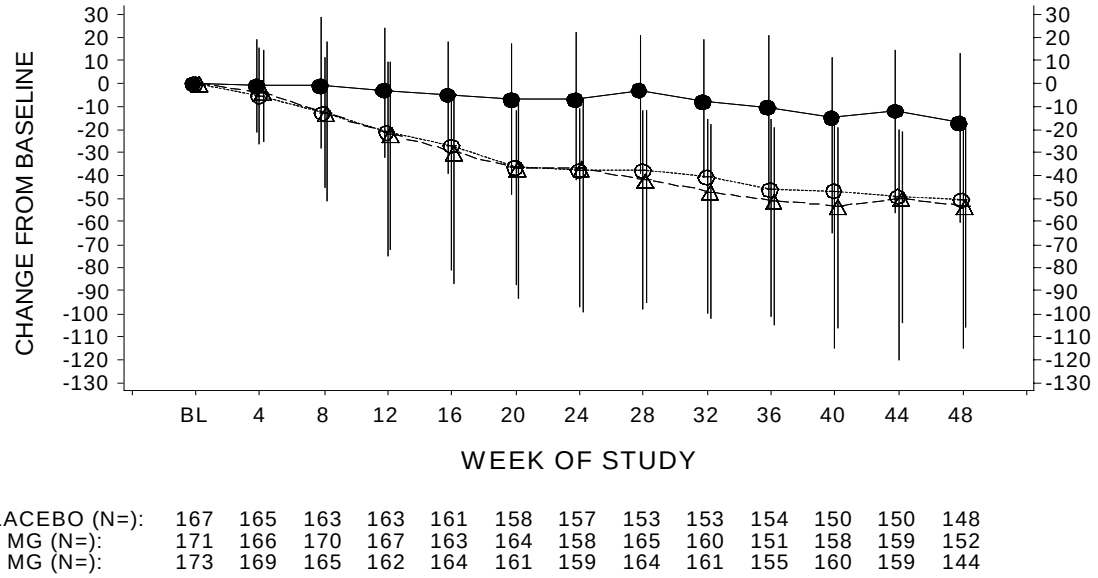
3.3. Effects on ALT Levels (0-48 weeks)

Further evidence of the activity of adefovir dipivoxil (10 mg, 30 mg) is demonstrated by the decreases in raised serum transaminase levels during 48 weeks of treatment (Table 3-5). For both adefovir dipivoxil treatment groups, there was a statistically significant difference in the proportion of patients with ALT normalization (defined as ALT level ≤ ULN) at week 48 compared with placebo. The median reduction from baseline at week 48 was 51 IU/L in the adefovir dipivoxil 10 mg treatment group and 54 IU/L in the adefovir dipivoxil 30 mg treatment group compared with 17 IU/L in the placebo group. The median changes in ALT during 48 weeks of treatment are displayed graphically in Figure 3-3.

Table 3-5. Change in ALT Levels at Week 48

	Placebo N = 167	**ADV 10 mg N = 171**	**ADV 30 mg N = 173**
ALT Level (Week 48)			
> ULN at Baseline*	164 (100%)	168 (100%)	169 (100%)
Normalized[a]	26 (16%)	81 (48%)	93 (55%)
Not Normalized	119 (73%)	70 (42%)	48 (28%)
Difference in proportion (95% CI [b])		32.4% (23.0% to 41.8%)	39.2% (29.8% to 48.5%)
p - value		< 0.001	< 0.001
Missing data[c]	19 (12%)	17 (10%)	28 (17%)
Change at Week 48 (IU/L)			
Mean ± SD	-23.01 ± 140.72	-92.06 ± 167.17	-74.44 ± 128.40
Median	-17	51	-54
Q1 to Q3	-60.5 to 13.0	-115.0 to –20.0	-106.0 to –16.5
N	148	152	144

Figure 3-3. Median and Interquartile Range of ALT Change (IU/L) from Baseline to Week 48 (ITT): Study 437



3.4. Patients with Seroconversion (0-48 Weeks)

Twenty patients in the adefovir dipivoxil 10 mg group (12%) and 23 patients in the adefovir dipivoxil 30 mg group (14%) demonstrated HBeAg seroconversion at week 48 compared with 9 patients in the placebo group (6%). The difference in proportions was statistically significant for both adefovir dipivoxil groups when compared with the placebo group (10 mg: $p < 0.05$, 30 mg: $p = 0.011$).

Loss of HBeAg (with or without development of anti-HBe) occurred in 24% of adefovir dipivoxil 10 mg patients, 27% of adefovir dipivoxil 30 mg patients, and 11% of placebo patients. The difference in proportions was again statistically significant for both adefovir dipivoxil groups when compared with the placebo group (10 mg: $p < 0.05$, 30 mg: $p < 0.01$). HBeAg seroconversion and HBeAg loss was associated with ALT normalization and HBV DNA suppression in the majority of patients in the active treatment arms compared with few patients in the placebo group.

Results of Safety Analyses

Summary tables of adverse events and laboratory data from the NDA are provided as follows:

Table 3-6 Overall Rates of Adverse Events and Discontinuations

Table 3-7 All Related Serious Adverse Events

Table 3-8 Adverse Events Reported in ≥ 5% of Patients in an Adefovir Dipivoxil Group During First 48 Weeks on Treatment

Table 3-9 Severe (Grade 3 or 4) Adverse Events Reported in ≥ 1% Patients in an Adefovir Dipivoxil Group

Table 3-10 All Adverse Events Leading to Discontinuation of Study Drug

Table 3-11 Laboratory Abnormalities and Maximum Grade of Toxicity

Table 3-6. Overall Rates of Adverse Events and Discontinuations

	Placebo (N = 167)		**ADV 10 mg (N = 171)**		**ADV 30 mg (N = 173)**	
	n	(%)	n	(%)	n	(%)
All Adverse Events	149	(89%)	148	(87%)	164	(95%)
Treatment-Related Adverse Events	93	(56%)	91	(53%)	124	(72%)
Serious Adverse Events	8	(5%)	9	(5%)	8	(5%)
Deaths	0	(0%)	0	(0%)	0	(0%)
Discontinuation Rate	13	(8%)	12	(7%)	14	(8%)
Discontinuations due to Adverse Events	1	(< 1%)	4	(2%)	5	(3%)

Table 3-7. All Related Serious Adverse Events

	Placebo (N = 167)	**ADV 10 mg (N = 171)**	**ADV 30 mg (N = 173)**
	n (%)	n (%)	n (%)
Number of Patients Experiencing Related Serious Adverse Events	1 (< 1%)	2 (1%)	3 (2%)
Abdominal Pain	0 (0%)	0 (0%)	1 (< 1%)
Fanconi-like Syndrome	0 (0%)	0 (0%)	1 (< 1%)
Myocardial Infarction	0 (0%)	0 (0%)	1 (< 1%)
ALT Increased	1 (< 1%)	1 (< 1%)	0 (0%)
AST Increased	0 (0%)	1 (< 1%)	0 (0%)
Chest Pain	0 (0%)	1 (< 1%)	0 (0%)

Table 3-8. Adverse Events Reported in ≥ 3% of Patients in Adefovir Dipivoxil Groups During First 48 Weeks on Treatment

	Placebo (N = 167)		ADV 10 mg (N = 171)		ADV 30 mg (N = 173)	
	n	(%)	n	(%)	n	(%)
Number of Patients with Adverse Events	149	(89%)	148	87%)	164	(95%)
Pharyngitis	54	(32%)	44	(26%)	70	(40%)
Headache	37	(22%)	43	(25%)	44	(25%)
Asthenia	32	(19%)	42	(25%)	45	(26%)
Abdominal Pain	32	(19%)	31	(18%)	38	(22%)
Flu syndrome	31	(19%)	28	(16%)	32	(18%)
Nausea	23	(14%)	17	(10%)	31	(18%)
Diarrhea	13	(8%)	23	(13%)	25	(14%)
Dyspepsia	14	(8%)	15	(9%)	19	(11%)
Pain	21	(13%)	19	(11%)	13	(8%)
Cough Increased	21	(13%)	11	(6%)	19	(11%)
Anorexia	9	(5%)	6	(4%)	18	(10%)
Back Pain	11	(7%)	11	(6%)	17	(10%)
Dizziness	13	(8%)	9	(5%)	18	(10%)
Flatulence	10	(6%)	13	(8%)	18	(10%)
Myalgia	18	(11%)	6	(4%)	13	(8%)
Rhinitis	19	(11%)	23	(13%)	13	(8%)
Fever	13	(8%)	10	(6%)	11	(6%)
Hypophosphatemia	2	(1%)	2	(1%)	11	(6%)
Rash	18	(11%)	6	(4%)	11	(6%)
Arthralgia	11	(7%)	10	(6%)	15	(9%)
Pruritus	11	(7%)	6	(4%)	8	(5%)
Vomiting	4	(2%)	8	(5%)	8	(5%)
Accidental injury	10	(6%)	8	(5%)	5	(3%)
ALT Increase	9	(5%)	8	(5%)	6	(3%)
Insomnia	10	(6%)	9	(5%)	9	(5%)
Somnolence	8	(5%)	8	(5%)	6	(3%)
Creatinine Increased	1	(< 1%)	6	(4%)	51	(29%)
Infection	7	(4%)	7	(4%)	6	(3%)
Depression	7	(4%)	7	(4%)	3	(2%)
Hematuria	2	(1%)	6	(4%)	3	(2%)

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Table 3-8. Adverse Events Reported in ≥ 3% of Patients in Adefovir Dipivoxil Groups During First 48 Weeks on Treatment (Continued)

	Placebo (N = 167)		ADV 10 mg (N = 171)		ADV 30 mg (N = 173)	
Dysuria	10	(6%)	3	(2%)	5	(3%)
Chest Pain	5	(3%)	5	(3%)	6	(3%)
Constipation	5	(3%)	5	(3%)	3	(2%)
Gastroenteritis	7	(4%)	5	(3%)	1	(< 1%)
Urinary Tract Infection	4	(2%)	2	(1%)	6	(3%)
Bronchitis	5	(3%)	2	(1%)	5	(3%)

Table 3-9. Severe (Grade 3 or 4) Adverse Events Reported in ≥ 1% Patients in an Adefovir Dipivoxil Group

	Placebo (N = 167)	ADV 10 mg (N = 171)	ADV 30 mg (N = 173)
	n (%)	n (%)	n (%)
Number of Patients Experiencing Severe Adverse Events	14 (8%)	17 (10%)	15 (9%)
Abdominal Pain	1 (< 1%)	0 (0%)	3 (2 %)
ALT Increased	3 (2%)	4 (2%)	2 (1%)
Hypophosphatemia	0 (0%)	0 (0%)	2 (1%)
AST Increased	0 (0%)	2 (1%)	1 (< 1%)
Headache	1 (< 1%)	2 (1%)	1 (< 1%)
Liver Function Tests Abnormal	1 (< 1%)	2 (1%)	1 (< 1%)
Chest Pain	0 (0%)	2 (1%)	0 (0%)
Pharyngitis	0 (0%)	2 (< 1%)	0 (0%)

Table 3-10. All Adverse Events Leading to Discontinuation of Study Drug

	Placebo (N = 167)	**ADV 10 mg (N = 171)**	**ADV 30 mg (N = 173)**
	n (%)	n (%)	n (%)
Number of Patients Discontinued Due to Adverse Event	1 (< 1%)	4 (2%)	5 (3%)
Abdominal Pain	0 (0%)	0 (0%)	1 (< 1%)
Amblyopia	0 (0%)	0 (0%)	1 (< 1%)
Creatinine Increased	0 (0%)	0 (0%)	1 (< 1%)
Fanconi-like Syndrome	0 (0%)	0 (0%)	1 (< 1%)
Headache	0 (0%)	0 (0%)	1 (< 1%)
Myocardial Infarction	0 (0%)	0 (0%)	1 (< 1%)
Nausea	1 (< 1%)	0 (0%)	1 (< 1%)
ALT Increased	0 (0%)	1 (< 1%)	0 (0%)
AST Increased	0 (0%)	1 (< 1%)	0 (0%)
Liver Function Test Abnormal	0 (0%)	1 (< 1%)	0 (0%)
Maculopapular Rash	0 (0%)	1 (< 1%)	0 (0%)
Pruritus	0 (0%)	1 (< 1%)	0 (0%)
Weight Loss	0 (0%)	1 (< 1%)	0 (0%)

Table 3-11. Laboratory Abnormalities and Maximum Grade of Toxicity

	Placebo		ADV 10 mg		ADV 30 mg	
Grade	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
ALT (X ULN)						
1 (1.25 to 2.5)	40	(24)	64	(38)	60	(35)
2 (> 2.5 to 5.0)	49	(29)	41	24)	54	(32)
3 (> 5.0 to 10)	42	(25)	29	(17)	25	(15)
4 (> 10)	32	(19)	17	(10)	14	(8)
AST (X ULN)						
1 (1.25 to 2.5)	62	(37)	72	(42)	80	(47)
2 (> 2.5 to 5.0)	45	(27)	32	(19)	30	(18)
3 (> 5.0 to 10)	31	(19)	14	(8)	19	(11)
4 (> 10)	13	(8)	5	(3)	3	(2)
Amylase (X ULN)						
1 (1.1 to 1.5)	34	(20)	21	(12)	28	(16)
2 (> 1.5 to 2.0)	8	(5)	8	(5)	8	(5)
3 (> 2.0 to 5.0)	6	(4)	7	(4)	4	(2)
4 (> 5.0)	0	(0)	0	(0)	0	(0)
Alk. Phosphatase (X ULN)						
1 (1.25 to 2.5)	11	(7)	11	(6)	27	(16)
2 (> 2.5 to 5.0)	0	(0)	1	(< 1)	1	(< 1)
3 (> 5.0 to 10)	0	(0)	0	(0)	1	(< 1)
4 (> 10)	0	(0)	0	(0)	0	(0)
Creatine Kinase (X ULN)						
1 (1.1 to 2.0)	31	(19)	54	(32)	45	(26)
2 (> 2.0 to 4.0)	22	(13)	21	(12)	19	(11)
3 (> 4.0 to 6.0)	5	(3)	8	(5)	5	(3)
4 (> 6.0)	5	(3)	7	(4)	10	(6)
Hypophosphatemia (mg/dL)						
1 (2.0–2.2)	8	(5%)	6	(4%)	15	(9%)
2 (1.5–< 2.0)	9	(5%)	4	(2%)	21	(12%)
3 (1.0–1.5)	0	(0%)	1	(< 1%)	5	(3%)
4 (< 1.0)	0	(0%)	0	(0%)	1	(< 1%)
Creatinine (mg/dL)						
1 (1.5 to 2.0)	0	(0%)	2	(1%)	17	(10%)
2 (> 2.0 to 3.0)	0	(0%)	0	(0%)	0	(0%)
3 (> 3.0 to 6.0)	0	(0%)	0	(0%)	0	(0%)
4 (> 6.0)	0	(0%)	0	(0%)	0	(0%)
Serum Bicarbonate (mEq/L)						
1 (16–17)	1	(< 1)	4	(2)	3	(2)
2 (11–15.9)	0	(0)	2	(1)	1	(< 1)
3 (8 to 10.9)	0	(0)	0	(0)	0	(0)
4 (< 8)	0	(0)	0	(0)	0	(0)

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Table 3-11. Laboratory Abnormalities and Maximum Grade of Toxicity (continued)

Grade	Placebo		ADV 10 mg		ADV 30 mg	
	n	(%)	n	(%)	n	(%)
Hyperglycemia (mg/dL)						
1 (116 to 160)	77	(46)	74	(44)	63	(37)
2 (161 to 250)	15	(9)	11	(6)	9	(5)
3 (251 to 500)	4	(2)	0	(0)	3	(2)
4 (> 500)	0	(0)	1	(< 1)	0	(0)
Hypoglycemia (mg/dL)						
1 (55 to 64)	16	(10)	17	(10)	20	(12)
2 (40 to 54)	4	(2)	1	(< 1)	8	(5)
3 (30 to 39)	0	(0)	0	(0)	0	(0)
4 (< 30)	0	(0)	0	(0)	1	(< 1)
Total Bilirubin (X ULN)						
1 (1.1–1.5)	7	(4%)	13	(8%)	12	(7%)
2 (> 1.5–2.5)	5	(3%)	6	(4%)	1	(< 1%)
3 (> 2.5–5.0)	2	(1%)	0	(0%)	1	(< 1%)
4 (> 5.0)	0	(0%)	0	(0%)	0	(0%)
Prothrombin Time (X ULN)						
1 (> .0–1.25)	7	(4%)	7	(4%)	6	(4%)
2 (> 1.25–1.5)	1	(< 1%)	1	(< 1%)	0	(0%)
3 (>1.5–3.0)	0	(0%)	1	(< 1%)	0	(0%)
4 (> 3.0)	0	(0%)	0	(0%)	1	(< 1%)
Hyponatremia (mEq/L)						
1 130 to 135	42	(25%)	22	(13%)	37	(22%)
2 (123 to 129)	2	(1%)	5	(3%)	1	(<1%)
3 (116 to 122)	0	(0%)	3	(2%)	1	(<1%)
4 (< 116)	1	(< 1%)	0	(0%)	0	(0%)
Hypernatremia (mEq/L)						
1 (146 to 150)	35	(21%)	47	(28%)	42	(25%)
2 (151 to 157)	1	(< 1%)	4	(2%)	0	(0%)
3 (158 to 165)	0	(0%)	0	(0%)	0	(0%)
4 (> 165)	0	(0%)	0	(0%)	0	(0%)
Hematuria						
1 < 10 RBCs	11	(7%)	11	(6%)	21	(12%)
2 10-100 RBCs	17	(10%)	18	(11%)	29	(17%)
3 > 100 RBCs	21	(13%)	21	(12%)	23	(13%)
4 Obstructive or Rx required	0	(0%)	0	(0%)	0	(0%)
Glycosuria						
1 (+1)	5	(3%)	1	(< 1%)	3	(2%)
2 (+2)	3	(2%)	1	(< 1%)	3	(2%)
3 (+3)	5	(3%)	1	(< 1%)	2	(1%)
4 (+4)	0	(0%)	0	(0%)	0	(0%)
Proteinuria (mg/dL)						
1 (< 100)	17	(10%)	24	(14%)	38	(22%)
2 (100 to 1,000)	11	(7%)	10	(6%)	23	(13%)
3 (> 1,000)	0	(0%)	0	(0%)	0	(0%)
4 (Nephrotic Syndrome)	0	(0%)	0	(0%)	0	(0%)

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Table 3-11. Laboratory Abnormalities and Maximum Grade of Toxicity (continued)

Grade	Placebo		ADV 10 mg		ADV 30 mg	
	n	(%)	n	(%)	n	(%)
Hypouricemia (mg/dL)						
1 (< 2.1 to ≥ 1.5)	1	(< 1%)	2	(1%)	7	(4%)
2 (< 1.5 to ≥ 1.0)	0	(0%)	0	(0%)	0	(0%)
3 (< 1.0 to ≥ 0.5)	0	(0%)	0	(0%)	0	(0%)
4 (< 0.5)	0	(0%)	0	(0%)	0	(0%)

Appendix 4. Phase 3 Open-Label Study in Liver Transplantation

4.1. Phase 3 Open-Label Study in Liver Transplantation Patients

Study 435, an open-label study in liver transplantation patients with chronic hepatitis B (both pre- and post-transplantation) with lamivudine-resistant HBV, was conducted to evaluate the efficacy and safety of adefovir dipivoxil in this population of medically compromised patients. The open-label design of study 435 is appropriate, because placebo-controlled trials would be unethical in this severely ill patient population who, as a result of recurrent hepatitis B, are at risk of loss of graft or death due to fibrosing cholestatic hepatitis. Currently, there is no suitable comparator therapy for lamivudine-resistant HBV.

4.1.1. Efficacy Results for Post-Liver Transplantation Cohort – NDA Reported Analyses

Efficacy data for the post-transplantation cohort (A) were available for reporting in the NDA. This population included both HBeAg positive and HBeAg negative patients, and patients with either compensated and decompensated liver disease including patients with significant medical comorbidities. Within cohort A, patients were enrolled into one of three subcohorts. Patients with adequate renal, hepatic, and hematologic function and no prior adefovir dipivoxil use were assigned to cohort 1. Cohort 2 included patients who were previously enrolled in study 451i in which they received open-label adefovir dipivoxil and hence they were durably suppressed at entry. Cohort 3 patients had either renal, hepatic, and/or hematologic dysfunction or other significant disease at baseline that precluded eligibility into cohort 1.

Data were reported for a total of 131 cohort A patients (cohort 1A = 79; cohort 2A = 10; cohort 3A = 42 patients, All Enrolled population) with a median duration of treatment with adefovir dipivoxil 10 mg of approximately 33 weeks. The majority of patients were male (86%) and white (80%) with a median age of 56 years. The genotypic analysis of baseline serum samples confirmed lamivudine-resistant YMDD HBV mutants in 98% of samples analyzed, thus confirming the clinical definition of lamivudine-resistance utilized in the study protocol to determine patient eligibility.

Table 4-1 presents the efficacy results for cohorts 1A and 3A. Cohort 2A are considered separately because of their prior exposure to adefovir dipivoxil.

In cohorts 1A and 3A, treatment with adefovir dipivoxil 10 mg resulted in rapid and statistically significant reductions in serum HBV DNA levels (as assessed by $DAVG_{24}$ and $DAVG_{48}$ and median changes from baseline) that were durable through 48 weeks. The reduction in serum HBV DNA in cohort 3A patients with significant medical comorbidities was similar to that seen in cohort 1A which enrolled patients predominantly with compensated liver disease.

Table 4-1. Overview of Efficacy Results: Study 435 (Post-Transplantation) Centrally Assessed Population

Efficacy Parameter	Cohort 1A (N = 68)		Cohort 3A (N = 33)	
Serum HBV DNA		**p-value**		**p-value**
Median $DAVG_{24}$ (log_{10} copies/mL)	-2.9	< 0.001	-2.9	< 0.001
Median $DAVG_{48}$ (log_{10} copies/mL)	-3.2	< 0.001	-3.3	< 0.001
Median change at week 24 (log_{10} copies/mL)	-3.5	< 0.001	-3.7	< 0.001
Median change at week 48 (log_{10} copies/mL)	-4.4	< 0.001	-3.9	< 0.001
Child-Pugh-Turcotte Score				
Median change in total score at week 24	0.0 (n = 21)	1.00	-2.0 (n = 14)	< 0.001
ALT				
Median change at week 24 (IU/L)	-37	< 0.001	-23	< 0.013
Median change at week 48 (IU/L)	-35	< 0.001	-43	< 0.001
Kaplan-Meier Estimate of Survival				
Survival at week 48*	99%	-	90%	-

* Kaplan-Meier estimates based on All Enrolled Population

As shown in Table 4-2, the antiviral response was consistent regardless of the baseline pattern of lamivudine-resistant HBV mutations.

Table 4-2. Change in Serum HBV DNA by Baseline Patterns of Lamivudine-Resistant HBV: Study 435

Baseline Pattern	Change in HBV DNA at Week 24[1] (Log_{10} copies/mL)		Number of Patients
	Mean	Median	
528M + 552V	- 4.0	- 3.7	41
521L + 528M + 552V	- 3.5	- 3.3	19
552I	- 3.6	- 3.8	9
528M + 552I	- 3.9	- 3.5	7
p-value	0.53		

1 Calculated for patients with both baseline and week 24 HBV DNA data.

Improvements were also demonstrated with respect to other secondary clinical and biochemical endpoints. Clinical response was confirmed by the statistically significant reduction from baseline in Child-Pugh-Turcotte score (in cohort 3A at week 24, and in the

combined cohorts at week 24 and 48, $p \leq 0.01$). The most dramatic improvements were observed in cohort 3A patients who had more significant decompensated liver disease at baseline. Overall normalization of ALT levels for the combined cohort A was observed in 61% of patients by week 48, comparable to the proportion to the patients who normalized ALT in studies 437 and 438 (see Table 8). Significant reductions from baseline were seen in serum bilirubin as well as significant increases from baseline in serum albumin.

Patients in cohort 2A who were previously treated with adefovir dipivoxil and had durable suppression of serum HBV DNA levels (median baseline level of 3.8 $\log_{10}$ copies/mL) also had additional reduction in serum HBV DNA at week 24, which was maintained at week 48 (median decrease -0.6 $\log_{10}$ copies/mL at both assessments, $p = 0.03$ at week 24, $p = 0.01$ at week 48). Since patients in cohort 2A were previously treated with adefovir dipivoxil, ALT levels were already reduced at baseline in this study and were sustained through week 48.

4.1.2. Updated Efficacy Results for Waitlisted and Post-Liver Transplantation Patients

Post-NDA, an updated evaluation provided efficacy results to support the risk-benefit assessment for patients participating in study 435 (submitted to FDA June 2002). Efficacy data for 196 cohort A and 128 cohort B patients, with median durations of treatment of 56.1 and 18.7 weeks, respectively, were included in this evaluation. The results of the updated analyses demonstrate similar antiviral and clinical benefits of treatment with adefovir dipivoxil 10 mg in patients waitlisted for transplantation (cohort B) as in patients treated post-liver transplantation (cohort A). These analyses also confirmed the antiviral and clinical benefits of longer-term treatment with adefovir dipivoxil in the post-liver transplantation cohort. An overview of the updated efficacy results is presented in Table 4-3.

Table 4-3. Overview of Results for Updated Efficacy Analysis (Safety Update Report): Study 435 (Post-Transplantation and Waitlisted for Liver Transplantation Patients)

Efficacy Parameter	Cohort A (N = 196) (Post-Transplantation)		Cohort B (N = 128) (Waitlisted)	
Serum HBV DNA		**p-value**		**p-value**
Median $DAVG_{24}$ (log_{10} copies/mL)	-3.1	< 0.001	-3.1	< 0.001
Median $DAVG_{48}$ (log_{10} copies/mL)	-3.3	< 0.001	-3.4	< 0.001
Median change at week 24 (log_{10} copies/mL)	-3.6	< 0.001	-3.7	< 0.001
Median change at week 48 (log_{10} copies/mL)	-4.3	< 0.001	-4.1	< 0.001
Median change at week 96 (log_{10} copies/mL)	-4.6	< 0.001	-	-
ALT				
Median change at week 24 (IU/L)	-29	< 0.001	-27.5	< 0.001
Median change at week 48 (IU/L)	-30	< 0.001	-37.0	< 0.001
Median change at week 96 (IU/L)	-42	< 0.001	-	-
% normalized before week 24 (IU/L)	48%	-	52%	-
% normalized before week 48 (IU/L)	63%	-	61%	-

Note: For all parameters except DAVG, all subcohorts (1-3) are combined. DAVG is presented for subcohorts 1 and 3 only.

Updated Kaplan-Meier estimates of survival were also reported. The Kaplan-Meier estimated proportion of post-liver transplantation patients surviving by week 48 in cohorts 1A, 2A, and 3A was 98%, 100%, and 82%, respectively. By week 96, the estimated proportion of these patients surviving in cohorts 1A, 2A, and 3A were 92%, 100%, and 82%, respectively. In patients waitlisted for transplantation, Kaplan-Meier estimates of survival by week 24 (median duration of treatment 18.7 weeks) were 89%, 100%, and 81% in cohorts 1B, 2B, and 3B, respectively. These survival rates are comparable to survival rates reported in the literature in liver transplantation patients with chronic hepatitis B treated with HBIg and lamivudine (or these treatments combined), and are significantly better than survival rates in patients with no treatment.[18, 20, 38]

In conclusion, the efficacy results of study 435 demonstrate the antiviral and clinical effectiveness of adefovir dipivoxil 10 mg once daily for the treatment of liver disease associated with lamivudine-resistant HBV in patients post-liver transplantation and waitlisted for transplantation.

4.1.3. Updated Safety Results for Waitlisted and Post-Liver Transplantation Patients

Deaths and Serious Adverse Events

A total of 42 (13%) deaths were reported in cohorts A (18 patients) and B (24 patients). All deaths in cohort A (post-liver transplantation patients) were assessed by the investigator to be due to complications of underlying HBV disease or post-operative complications and not related to adefovir dipivoxil. In cohort B (patients waitlisted for liver transplantation), with the exceptions of multiorgan failure (relationship unknown) and hepatorenal syndrome (possibly related), deaths were assessed by the investigator to be unrelated to treatment.

In the case of hepatorenal syndrome, pre-existing medical conditions were significant for hepatic encephalopathy and esophageal varices, and baseline liver function test abnormalities included transaminase elevations, bilirubin that increased from 194 μmol/L to 456 μmol/L within 2 days prior to administration of study drug, albumin 20 g/L, and prothrombin time 23.6 seconds. The patient developed hepatorenal syndrome secondary to end-stage hepatitis B-related cirrhosis and died following a month of adefovir dipivoxil therapy. The investigator considered that the progression of liver disease to be related to a fulminant course of hepatitis, and the primary cause of the hepatorenal syndrome and subsequent death due to the end-stage hepatitis B-related cirrhosis, but could not rule out the study drug as a possible contributory factor.

Overall, there was a low rate of related serious adverse events (5% in cohort A, 4% in cohort B) and adverse events leading to drug discontinuation (5% in cohort A, 6% in cohort B).

In post-liver transplantation patients (cohort A), serious adverse events were reported in 49 patients (25%); events in all but 7 patients were assessed as unrelated to study drug. Eleven serious adverse events in 7 (4%) patients were considered by the investigator to be possibly or probably related to adefovir dipivoxil, and included: ALT elevation, fever, abnormal liver function, abdominal pain, nausea, vomiting, dehydration, thrombocytopenia, acute renal failure, hyperkalemia, and increased creatinine.

In patients waitlisted for liver transplantation (cohort B), serious adverse events were reported in 37 patients (29%); however, 95% of these events were assessed as unrelated to adefovir dipivoxil. Seven serious hepatic events in 6 (5%) patients were assessed by the investigator as possibly or probably related to adefovir dipivoxil, specifically: hepatitis B reactivation, hepatorenal syndrome, ALT elevation, AST elevation, elevated bilirubin (2 patients), and cholangitis.

Seven of 9 patients (5%) who discontinued in cohort A had serious adverse events; all but one case (thrombocytopenia) were considered unrelated to study drug. Three patients (2%) discontinued drug for renal adverse events; all 3 renal events were assessed by the investigator as unrelated to study drug. The eight patients (6%) who discontinued treatment in cohort B all had serious adverse events. All but one case in a cohort 3B patient (liver function abnormal) were considered unrelated to study drug.

The profile of deaths, SAEs, and discontinuations due to adverse events in this population of liver transplantation patients who were failing lamivudine therapy is consistent with that reported in similar transplantation populations in the presence of recurrent HBV and significant comorbidities. In one multicenter, open label study, in which liver transplantation candidates received open label lamivudine 100 mg daily before and after liver transplantation for chronic hepatitis B, 6 deaths (15%) were reported in the post-transplant cohort patients (median time on study of 38 months).[38] Causes of death were graft vs. host disease, myocardial infarction, cardiovascular collapse, multisystem organ failure, recurrent HCC, and recurrent HBV infection complicated by spontaneous bacterial peritonitis. Deaths were attributed to complications of advanced liver disease. In a separate report of 52 patients with chronic hepatitis B after liver transplantation treated with open label lamivudine 100 mg daily, 4 patients (8%) discontinued due to adverse events. Two patients died (1 each of hepatorenal failure and HCC).[19]

Targeted Evaluation of Serum Creatinine and Serum Phosphorus

Graded Abnormalities:
In post-liver transplantation patients (cohort A), 41 (21%) of 191 evaluable patients with baseline serum creatinine had a grade 1 or higher baseline serum creatinine, indicative of baseline renal insufficiency in these patients. In these patients, grade 3 or 4 serum creatinine toxicity (serum creatinine ≥ 3.0 mg/dL) was reported in 8 (4%) of 191 evaluable patients; however, 7 of these patients had pre-existing renal insufficiency at baseline (median baseline serum creatinine 2.4 mg/dL, range 1.5 to 5.4 mg/dL). One (1%) patient in cohort 3A had a confirmed serum phosphorus < 1.5 mg/dL (grade 3). This 66-year-old male patient had a history of hypertension and had a calculated creatinine clearance at baseline of 57.5 mL/min. With the recent dosing guidelines derived from pharmacokinetic study 473 (see Appendix 2), this patient would have been dosed differently with dose interval adjustment for creatinine clearance < 50 mL/min during the study. No patients in cohort A had grade 4 hypophosphatemia.

Of the 119 evaluable patients in cohort B (waitlisted for liver transplantation), 7 (6%) had grade 1 or higher serum creatinine at baseline. Grade 3 or 4 serum creatinine toxicity (serum creatinine ≥ 3.0 mg/dL) was reported in 6 (5%) of 119 evaluable patients; however, 3 (50%) of these patients had pre-existing renal insufficiency at baseline (serum creatinine at baseline was grade 3 in 1 patient, grade 4 in two patients). Two (2%) patients waitlisted for liver transplantation had serum phosphorus < 1.5 mg/dL that were not confirmed with two consecutive laboratory assessments.

Changes from Baseline:
In cohort A, there was no median change in serum phosphorus from baseline at weeks 48 and 96. A median increase in serum creatinine of 0.1 mg/dL was seen by week 48 and was sustained through week 96 in cohort A patients. In cohort B, there was a median increase in serum phosphorus from baseline of 0.2 mg/dL at week 24 and 0.3 mg/dL by week 48, and a median increase in serum creatinine of 0.1 mg/dL at week 24 and 0.2 mg/dL by week 48.

Kaplan-Meier Estimates of Renal Abnormalities:
Kaplan-Meier estimates of confirmed changes in serum creatinine (≥ 0.5 mg/dL) from baseline were observed in 12%, 0%, and 15 % of post-liver transplantation patients in cohorts 1A, 2A, and 3A by week 48. By week 96, this estimate increased to 22%, 13%, and 33% of patients, respectively. These changes in serum creatinine were generally of mild to moderate severity. One (1%) patient had a confirmed serum phosphorus < 1.5 mg/dL at week 56 which resolved with continued treatment (described above).

In patients waitlisted for liver transplantation, the Kaplan-Meier estimate of patients with confirmed serum creatinine increase ≥ 0.5 mg/dL from baseline was 26%, 0%, and 30% by week 48. No patient had a confirmed serum phosphorus < 1.5 mg/dL on this cohort.

Discontinuations Due to Renal Event:
Overall, 4 of 324 (1%) patients in the combined A and B cohorts discontinued treatment with adefovir dipivoxil 10 mg following changes in renal function (all four were post-liver transplantation patients). The remaining patients with renal adverse events continued treatment at a reduced daily dose (5 mg) or reduced dosing interval (every other day). In these patients, the risks of continuing treatment with adefovir dipivoxil were outweighed by the benefits of treatment, including prevention of recurrent hepatitis B and subsequent loss of liver graft in liver transplantation patients, and prevention of progressive liver disease and death in patients waitlisted for liver transplantation.

Assessment of Risks for Renal Dysfunction:
To assist in the interpretation of the observed serum creatinine changes, patients in study 435 with a treatment-emergent confirmed increase in serum creatinine of ≥ 0.5 mg/dL above baseline were individually assessed. Of the 38 patients (26 in cohort A, 12 in cohort B) who met this criteria, all had at least one (and in many cases several) baseline characteristics that would put them at risk for changes in renal function. These risk factors included varying degrees of pre-existing renal insufficiency at baseline, decompensated liver disease as indicated by a Child-Pugh-Turcotte score of ≥ 7 and other significant concurrent illnesses including hypertension, diabetes, and renal disease. In addition, most patients (98%) were taking concomitant immunosuppressant agents (cyclosporine or tacrolimus) which are known to be nephrotoxic.[79-81] In many cases the immunosuppressants had been taken for long periods since 85% had their transplant more than one year prior to baseline. Furthermore, 15 patients with normal serum creatinine at baseline had elevated baseline serum bilirubin levels, which is known to mask laboratory changes indicative of renal impairment.[82]

Since renal adverse events accounted for only 1% of discontinuations due to adverse events in this study, almost all patients remained on treatment after the serum creatinine elevation. In 6 of the 38 patients (16%) with confirmed, serum creatinine increase ≥ 0.5 mg/dL from baseline, the abnormality had resolved as of last follow-up. In the remaining 32 patients, 18 had stable serum creatinine (serum creatinine ± 0.2 mg/dL of the confirmed serum creatinine ≥ 0.5 mg/dL from baseline), 5 had improved serum creatinine (≤ 0.3 mg/dL of the confirmed serum creatinine ≥ 0.5 mg/dL increase from baseline but not yet resolved to ≤ 0.3 mg/dL from baseline) as of last laboratory follow-up, and 9 had worsened serum

creatinine (serum creatinine ≥ 0.3 mg/dL above the confirmed serum creatinine ≥ 0.5 mg/dL from baseline).

In summary, while interpretation of these data is complicated, individual patient details demonstrate serum creatinine changes occurred in liver transplantation patients with numerous risk factors for changes in renal function. The changes in renal function may have been due to pre-existing renal disease and/or drug-induced renal dysfunction related to the concomitant immunosuppressant agents or other nephrotoxic drugs. Importantly, a significant proportion of liver transplantation patients with changes in serum creatinine in study 435 would now be managed differently in light of the results of a pharmacokinetic study of adefovir dipivoxil 10 mg in patients with varying degrees of renal impairment (study 473). Results of this study have led to recommendations for dose interval adjustment in patients with moderate to severe renal insufficiency (creatinine clearance < 50 mL/min), as provided in Appendix 2.

4.1.4. Other Adverse Events of Special Interest in Study 435

As of NDA safety update, 60 of the following serious renal and hepatic adverse events were reported in 44 patients in study 435, renal failure (16 patients, 4 possibly related to adefovir dipivoxil), creatinine increase (1 patient, possibly related), encephalopathy (14 patients, all unrelated), liver failure (17 patients, all unrelated), multiorgan failure (3 patients, all possibly related), and hepatorenal syndrome (4 patients, 1 possibly related). Six patients had 9 serious renal and hepatic events, as noted above, assessed by the investigator to be possibly related to adefovir dipivoxil which are further described below.

Of the four patients with renal failure assessed by the investigator as possibly related to adefovir dipivoxil (2 patients each in the waitlisted and post-liver transplantation cohorts), each had one or more identified risk factors for the development or worsening of renal impairment. These risk factors included: pre-existing renal impairment at baseline or history of renal dysfunction or failure (all 4 cases), hypertension (2), concomitant nephrotoxic immunosuppressants (2), unstable decompensating liver disease just prior to initiation of adefovir dipivoxil (2), paracentesis with 15 liters of ascitic fluid drained in a one week period just prior to the event (1), Enterococcal and Staphylococcal bacteremia (1), *Clostridium difficile* diarrhea temporally related to onset of renal dysfunction (1), chronic liver graft rejection (1), and acute bleeding of esophageal varices temporal to the event (1).

One post-liver transplantation patient with history of chronic renal insufficiency and hypertension developed a serum creatinine increase assessed by a renal consultant as prerenal azotemia following diarrhea from aggressive colchicine therapy for acute gout; however the role of adefovir dipivoxil could not be completely excluded.

Hepatorenal syndrome was reported as possibly related to adefovir dipivoxil in one patient with history of liver cirrhosis complicated with hepatic encephalopathy and esophageal varices who was waitlisted for liver transplantation at study entry. The patient developed hepatorenal syndrome following 4 weeks of adefovir dipivoxil treatment secondary to end-stage hepatitis B-related cirrhosis and subsequently died. The investigator assessed that the progression of liver disease was related to a fulminant course of hepatitis despite the use of

adefovir dipivoxil and would have occurred regardless of treatment, and that the death was due to end-stage hepatitis B-related cirrhosis, but he could not completely exclude adefovir dipivoxil as a possible contributory factor.

4.1.5. Conclusions for Study 435

Overall, the efficacy results of study 435 demonstrate the antiviral and clinical effectiveness of adefovir dipivoxil 10 mg once daily and are consistent with that seen in patients with compensated liver disease and HBeAg + and HBeAg – chronic hepatitis B. The treatment was generally well tolerated in this group of 324 severely medically compromised chronic hepatitis B patients who were either waitlisted for or post-liver transplantation with lamivudine-resistant HBV. There was a low incidence of discontinuations due to adverse events and a low incidence of serious related adverse events. Changes in serum creatinine were observed in a proportion of the liver transplantation population with multiple risk factors for changes in renal function. The serum creatinine changes were generally mild in nature and very few patients discontinued due to renal events. In patients waitlisted and post-liver transplantation who are at high risk of disease progression and/or liver graft loss and death if recurrent hepatitis B is not controlled, new recommendations for dose interval adjustments will allow treatment with adefovir dipivoxil to be initiated at an appropriate dose for renal impairment present at baseline, and to be continued with dose interval adjustment in patients with changes in renal function during treatment. While the impact of these new dosing guidelines still has to be evaluated, there is a highly favorable risk/benefit profile supporting treatment of these very sick patients.

Appendix 5. NDA Integrated Safety Analyses (Studies 437 and 438): Summary Tables of Adverse Events and Laboratory Abnormalities

Table 5-1. Adverse Events (≥ 3% of Patients in the All Adefovir Dipivoxil 10 mg Group): Studies 437 and 438 (NDA Cutoff)

	Placebo (0-48 Weeks) (N = 228)		ADV 10 mg (0-48 Weeks) (N = 294)		All ADV 10 mg (0-96 Weeks) (N = 492)	
Adverse Event	n	(%)	n	(%)	n	(%)
No. with Adverse Events	194	(85%)	242	(82%)	340	(69%)
Headache	47	(21%)	72	(24%)	92	(19%)
Pharyngitis	68	(30%)	67	(23%)	89	(18%)
Asthenia	42	(18%)	58	(20%)	75	(15%)
Abdominal Pain	35	(15%)	49	(17%)	75	(15%)
Flu Syndrome	44	(19%)	41	(14%)	55	(11%)
Rhinitis	20	(9%)	29	(10 %)	42	(9%)
Pain	27	(12%)	29	(10%)	39	(8%)
Diarrhea	15	(7%)	28	(10%)	33	(7%)
Nausea	25	(11%)	22	(7%)	30	(6%)
Back pain	15	(7%)	23	(8%)	29	(6%)
Cough Increased	25	(11%)	21	(7%)	28	(6%)
Dyspepsia	16	(7%)	21	(7%)	25	(5%)
Insomnia	14	(6%)	15	(5%)	23	(5%)
Flatulence	12	(5%)	18	(6%)	20	(4%)
Fever	16	(7%)	15	(5%)	20	(4%)
Accidental Injury	12	(5%)	12	(4%)	16	(3%)
Myalgia	19	(8%)	10	(3%)	16	(3%)
ALT Increased	12	(5%)	9	(3%)	15	(3%)
Rash	18	(8%)	7	(2%)	15	(3%)
Arthralgia	13	(6%)	11	(4%)	14	(3%)
Dizziness	14	(6%)	11	(4%)	14	(3%)
Vomiting	5	(2 %)	12	(4%)	14	(3%)

Table 5-2. Incidence of Grade 3 or Higher Adverse Events (≥ 2 Patients in the All Adefovir Dipivoxil 10 mg Group): Studies 437 and 438 (NDA Cutoff)

Adverse Event	Placebo (0-48 Weeks) (N = 228)		ADV 10 mg (0-48 Weeks) (N = 294)		All ADV 10 mg (0-96 Weeks) (N = 492)	
	n	(%)	n	(%)	N	(%)
Number with ≥ Grade 3 Event	20	(9%)	24	(8%)	33	(7%)
ALT Increase	5	(2%)	4	(1%)	5	(1%)
Headache	2	(< 1%)	2	(< 1%)	4	(< 1%)
Pharyngitis	0	(0%)	3	(1%)	3	(< 1%)
AST Increase	1	(< 1%)	2	(< 1%)	3	(< 1%)
Abdominal Pain	1	(< 1%)	1	(< 1%)	2	(< 1%)
Chest Pain	0	(0%)	2	(< 1%)	2	(< 1%)
HIV Test Positive	0	(0%)	1	(< 1%)	2	(< 1%)
Liver Function Tests Abnormal	1	(< 1%)	2	(< 1%)	2	(< 1%)
Pruritus	0	(0%)	1	(< 1%)	2	(< 1%)

Table 5-3. Changes in Laboratory Parameters: Studies 437 and 438 (NDA Cutoff)

Laboratory Parameter	Placebo (0-48 Weeks)	ADV 10 mg (0-48 Weeks)	All ADV 10 mg (0-96 Weeks)
ALT (IU/L)			
Baseline (N)	228	294	492
Mean ± SD	141.89 ± 150.58	140.74 ± 142.23	125.84 ± 128.67
Median	97.50	95.00	84.00
Q1 to Q3	70.50 to 160.50	66.00 to 165.00	56.50 to 149.00
Change at Week 48 (N)	202	268	277
Mean ± SD	-37.50 ± 165.24	-95.84 ± 149.86	-93.65 ± 148.64
Median	-22.00	-52.00	-52.00
Q1 to Q3	-66.00 to 6.00	-129.00 to –21.00	-127.00 to -21.00
Alkaline Phosphatase (mg/dL)			
Baseline (N)	228	294	492
Mean ± SD	76.27 ± 23.83	80.21 ± 27.90	78.33 ± 26.34
Median	72.50	77.00	74.00
Q1 to Q3	59.00 to 88.00	62.00 to 92.00	61.00 to 91.00
Change at Week 48 (N)	203	268	277
Mean ± SD	-1.28± 15.78	-4.35± 19.14	-4.25 ± 18.92
Median	0.00	-3.00	-3.00
Q1 to Q3	-11.00 to 7.00	-12.00 to 7.00	-12.00 to 7.00
Total Bilirubin (mg/dL)			
Baseline (N)	228	294	492
Mean ± SD	0.67 ± 0.35	0.69 ± 0.40	0.66 ± 0.38
Median	0.60	0.60	0.60
Q1 to Q3	0.50 to 0.80	0.50 to 0.80	0.40 to 0.80
Change at Week 48 (N)	202	268	277
Mean ± SD	-0.05 ± 0.26	-0.07 ± 0.35	-0.07 ± 0.35
Median	-0.10	-0.10	-0.10
Q1 to Q3	-0.20 to 0.10	-0.20 to 0.10	-0.20 to 0.10
Prothrombin Time (sec)			
Baseline (N)	226	290	488
Mean ± SD	12.48 ± 0.76	12.44 ± 1.02	12.37 ± 0.96
Median	12.40	12.30	12.30
Q1 to Q3	11.90 to 12.90	11.80 to 12.90	11.80 to 12.80
Change at Week 48 (N)	189	247	255
Mean ± SD	-0.19 ± 0.07	-0.25 ± 0.90	-0.25 ± 0.89
Median	-0.20	-0.20	-0.20
Q1 to Q3	-0.60 to 0.20	-0.70 to 0.30	-0.70 to 0.30

Table 5-3. Changes in Laboratory Parameters: Studies 437 and 438 (NDA Cutoff) (continued)

Laboratory Parameter	Placebo (0-48 Weeks)	ADV 10 mg (0-48 Weeks)	All ADV 10 mg (0-96 Weeks)
Albumin (g/dL)			
Baseline (N)	228	294	492
Mean ± SD	4.03 ± 0.36	4.05 ± 0.38	4.03 ± 0.37
Median	4.00	4.00	4.00
Q1 to Q3	3.80 to 4.20	3.80 to 4.30	3.80 to 4.30
Change at Week 48 (N)	202	268	277
Mean ± SD	-0.02 ± 0.32	0.11 ± 0.36	0.11 ± 0.36
Median	0.00	0.10	0.10
Q1 to Q3	-0.20 to 0.20	-0.10 to 0.30	-0.10 to 0.30
Serum creatinine (mg/dL)			
Baseline (N)	228	294	492
Mean ± SD	0.80 ± 0.17	0.81 ± 0.16	0.81 ± 0.16
Median	0.80	0.80	0.80
Q1 to Q3	0.70 to 0.90	0.70 to 0.90	0.70 to 0.90
Change at Week 48 (N)	203	268	277
Mean ± SD	0.01 ± 0.12	0.04 ± 0.14	0.04 ± 0.13
Median	0.00	0.00	0.00
Q1 to Q3	-0.10 to 0.10	0.00 to 0.10	0.00 to 0.10
Serum phosphorus (mg/dL)			
Baseline (N)	228	294	492
Mean ± SD	3.42 ± 0.58	3.36 ± 0.60	3.41 ± 0.59
Median	3.45	3.40	3.40
Q1 to Q3	3.00 to 3.80	2.90 to 3.80	3.00 to 3.80
Change at Week 48 (N)	203	268	277
Mean ± SD	0.07 ± 0.68	0.03 ± 0.64	0.02 ± 0.64
Median	0.10	0.05	0.10
Q1 to Q3	-0.30 to 0.50	-0.30 0.50	-0.30 to 0.50

Table 5-4. Maximum Grade of Laboratory Toxicity (Selected Laboratory Parameters): Studies 437 and 438 (NDA Cutoff)

	Placebo (0-48 Weeks)		ADV 10 mg (0-48 Weeks)		All ADV 10 mg (0-96 Weeks)	
Laboratory Parameter	n/N	(%)	n/N	(%)	n/N	(%)
ALT (x ULN)						
1 1.25 to 2.5	53/228	(23%)	113/293	(39%)	178/490	(36%)
2 > 2.5 to 5.0	73/228	(32%)	63/293	(22%)	104/490	(21%)
3 > 5.0 to 10	55/228	(24%)	40/293	(14%)	63/490	(13%)
4 > 10	39/228	(17%)	19/293	(6%)	25/490	(5%)
AST (x ULN)						
1 1.25 to 2.5	89/228	(39%)	122/293	(42%)	197/490	(40%)
2 > 2.5 to 5.0	65/228	(29%)	51/293	(17%)	82/490	(17%)
3 > 5.0 to 10	35/228	(15%)	18/293	(6%)	28/490	(6%)
4 > 10	18/228	(8%)	5/293	(2%)	7/490	(1%)
Total Bilirubin (x ULN)						
1 1.1 to 1.5	13/228	(6%)	19/293	(6%)	31/490	(6%)
2 > 1.5 to 3.0	8/228	(4%)	14/293	(5%)	18/490	(4%)
3 > 3.0 to 10	5/228	(2%)	1/293	(<1%)	2/490	(<1%)
4 > 10	0/228	(0%)	0/293	(0%)	0/490	(0%)
Alk. Phosphatase (x ULN)						
1 1.25 to 2.5	19/228	(8%)	23/293	(8%)	33/491	(7%)
2 > 2.5 to 5.0	0/228	(0%)	1/293	(<1%)	2/491	(<1%)
3 > 5.0 to 10	0/228	(0%)	0/293	(0%)	0/491	(0%)
4 > 10	0/228	(0%)	0/293	(0%)	0/491	(0%)
Prothrombin Time						
1 (1.25 to 2.5)	10/227	(4%)	11/293	(4%)	21/491	(4%)
2 (> 2.5 to 5.0)	1/227	(<1%)	1/293	(<1%)	2/491	(<1%)
3 (> 5.0 to 10)	0/227	(0%)	2/293	(<1%)	2/491	(<1%)
4 (> 10)	0/227	(0%)	0/293	(0%)	0/491	(0%)
Creatine Kinase (x ULN)						
1 1.1 to 2.0	50/228	(22%)	91/293	(31%)	137/490	(28%)
2 > 2.0 to 4.0	27/228	(12%)	41/293	(14%)	56/490	(11%)
3 > 4.0 to 6.0	7/228	(3%)	12/293	(4%)	14/490	(3%)
4 > 6.0	8/228	(4%)	9/293	(3%)	13/490	(3%)
Amylase (x ULN)						
1 1.1 to 1.5	44/228	(19%)	51/293	(17%)	79/491	(16%)
2 > 1.5 to 2.0	12/228	(5%)	15/293	(5%)	24/491	(5%)
3 > 2.0 to 5.0	8/228	(4%)	11/193	(4%)	16/491	(3%)
4 > 5.0	1/228	(<1%)	0/293	(0%)	1/491	(<1%)
Hyperglycemia (mg/dL)						
1 116 to 160	91/228	(40%)	115/293	(39%)	162/490	(33%)
2 161 to 250	22/228	(10%)	25/293	(9%)	41/490	(8%)
3 251 to 500	5/228	(2%)	2/293	(<1%)	4/490	(<1%)
4 > 500	0/228	(0%)	1/293	(<1%)	1/490	(<1%)

Table 5-4. Maximum Grade of Laboratory Toxicity (Selected Laboratory Parameters): Studies 437 and 438 (NDA Cutoff) (continued)

	Placebo (0-48 Weeks)		ADV 10 mg (0-48 Weeks)		All ADV 10 mg (0-96 Weeks)	
Laboratory Parameter	n/N	%	n/N	%	n/N	%
Hypoglycemia (mg/dL)						
1 55 to 64	20/228	(9%)	24/293	(8%)	32/490	(7%)
2 40 to 54	5/228	(2%)	5/293	(2%)	15/490	(3%)
3 30 to 39	0/228	(0%)	0/293	(0%)	0/490	(0%)
4 < 30	0/228	(0%)	0/293	(0%)	0/490	(0%)
Creatinine (mg/dL)						
1 1.5 to 2.0	0/228	(0%)	3/293	(1%)	3/491	(<1%)
2 2.1 to 3.0	0/228	(0%)	0/293	(0%)	1/491	(<1%)
3 3.1 to 6.0	0/228	(0%)	0/293	(0%)	0/491	(0%)
4 > 6.0	0/228	(0%)	0/293	(0%)	0/491	(0%)
Hypophosphatemia (mg/dL)						
1 2.0 to 2.2	9/228	(4%)	12/293	(4%)	22/491	(4%)
2 1.5 to 1.9	10/228	(4%)	8/293	(3%)	15/491	(3%)
3 1.0 to 1.4	0/228	(0%)	1/293	(<1%)	1/491	(<1%)
4 < 1.0	0/228	(0%)	0/293	(0%)	0/491	(0%)
Hyponatremia (mEq/L)						
1 130 to 135	46/228	(20%)	29/293	(10%)	36/491	(7%)
2 123 to 129	2/228	(<1%)	5/293	(2%)	5/491	(1%)
3 116 to 122	0/228	(0%)	3/293	(1%)	3/491	(<1%)
4 < 116	1/228	(<1%)	1/293	(<1%)	1/491	(<1%)
Hypernatremia (mEq/L)						
1 146 to 150	51/228	(22%)	80/293	(27%)	122/491	(25%)
2 151 to 157	1/228	(<1%)	5/293	(2%)	6/491	(1%)
3 158 to 165	0/228	(0%)	0/293	(0%)	2/491	(<1%)
4 > 165	0/228	(0%)	0/293	(0%)	0/491	(0%)
Hypouricemia (mg/dL)						
1 ≥ 1.5 to < 2.1	1/228	(<1%)	2/293	(<1%)	2/491	(<1%)
2 ≥ 1.0 to < 1.5	0/228	(0%)	0/293	(0%)	0/490	(0%)
3 ≥ 0.5 to < 1.0	0/228	(0%)	0/293	(0%)	0/490	(0%)
4 < 0.5	0/228	(0%)	0/293	(0%)	0/490	(0%)
Glycosuria						
1 1+	7/228	(3%)	2/293	(<1%)	7/490	(1%)
2 2+	4/228	(2%)	3/293	(1%)	2/490	(<1%)
3 3+	6/228	(3%)	4/293	(1%)	9/490	(2%)
4 4	0/228	(0%)	0/293	(0%)	0/490	(0%)
Hematuria						
1 < 10 RBCs	22/227	(10%)	26/293	(9%)	37/490	(8%)
2 10 to 100 RBCs	25/227	(11%)	32/293	(11%)	50/490	(10%)
3 > 100 RBCs	23/227	(10%)	31/293	(11%)	42/490	(9%)
4 Obstructive	0/227	(0%)	0/293	(0%)	0/490	(0%)
Proteinuria (mg/dL)						
1 1+	24/228	(11%)	39/293	(13%)	51/490	(10%)
2 2+ to 3+	12/228	(5%)	17/293	(6%)	24/490	(5%)
3 4+	0/228	(0%)	0/293	(0%)	0/490	(0%)
4 Nephrotic syndrome	0/228	(0%)	0/293	(0%)	0/490	(0%)

Appendix 6. Assessment of Renal Toxicity at Higher Doses (≥ 30 mg) of Adefovir Dipivoxil

Adefovir dipivoxil has been administered chronically at doses of 30 mg daily in 212 patients with chronic hepatitis B (study 412 extension/maintenance and study 437), and at doses of 60 mg and 120 mg daily in over 10,000 patients with HIV infection treated in clinical studies and expanded access programs. The principal dose related toxicity observed in these studies at higher doses is nephrotoxicity. In HIV-infected patients, the risk for development and maximum severity of renal abnormalities was significantly less in patients treated with adefovir dipivoxil 60 mg daily than in those who received adefovir dipivoxil 120 mg.

Analyses of the changes in renal parameters in these studies revealed that an increase in serum creatinine of ≥ 0.5 mg/dL from baseline or a decrease in serum phosphorus to < 1.5 mg/dL, as confirmed by two consecutive laboratory assessments, were the most sensitive and specific indicators of adefovir related nephrotoxicity. Other laboratory abnormalities, such as proteinuria, glycosuria, or decreased urine bicarbonate occurred in patients with adefovir related nephrotoxicity but were much less specific or sensitive.

Table 6-1 compares the incidence of unconfirmed serum creatinine and serum phosphorus abnormalities that were reported in studies of higher doses of adefovir dipivoxil with the results of the integrated safety analyses for adefovir dipivoxil 10 mg in chronic hepatitis B patients. The doses of adefovir dipivoxil examined include the 120 mg daily dose administered to HIV-infected patients in study GS-96-408 (study 408) and doses of 60 mg and 120 mg daily administered to HIV-infected patients in study GS-97-417 (study 417). In patients with chronic hepatitis B, the 30 mg dose administered to patients in study 437 is also included. Note that in the HIV studies, the serum phosphorus cut-off for Kaplan-Meier estimates was < 2.0 mg/dL (grade 2) compared with < 1.5 mg/dL used in the integrated safety analysis for studies 437 and 438 (see Section 6.2.3). Therefore, for comparative purposes, additional Kaplan-Meier estimates for the integrated safety analyses (adefovir dipivoxil 10 mg in chronic hepatitis B) of serum phosphorus based on the 2.0 mg/dL cutoff are presented.

Of the HIV-infected studies, study 408 was a randomized, double-blind, placebo-controlled study of adefovir dipivoxil 120 mg versus placebo when added to standard antiretroviral therapy for 48 weeks in the treatment of HIV-infected patients. Patients were randomized to receive either blinded adefovir dipivoxil 120 mg or placebo orally once daily for 24 weeks in addition to their current antiretroviral therapy and then continued open-label adefovir dipivoxil 120 mg daily for an additional 24 weeks (48 weeks total). The other study in HIV-infected patients, study 417 was a randomized, double-blind study of adefovir dipivoxil 60 mg and 120 mg when administered in combination with nelfinavir and/or saquinavir SGC plus one of three other licensed reverse transcriptase inhibitors (RTIs) for treatment of HIV-infected, protease inhibitor-naïve adults over 48 weeks of treatment.

Table 6-1. Incidence of Renal Laboratory Abnormalities (Unconfirmed Events) in Adefovir Dipivoxil HIV and Chronic HBV Studies

Study	Indication	ADV (mg)	N	Serum Creatinine ≥ 0.5 mg/dL from Baseline	Serum Phosphorus < 2.0 mg/dL
				K-M Estimate	K-M Estimate
408	HIV	120	403	42% at wk 48	44% at wk 48
417	HIV	120	104	42% at wk 50	49% at wk 50
417	HIV	60	108	34% at wk 50	26% at wk 50
437	Chronic hepatitis B	30	173	21% at wk 48	16% at wk 48
437/438 (0-48 weeks)*	Chronic hepatitis B	10	294	1% at wk 48	3% at wk 48
437/438 (0-48 weeks)*	Chronic hepatitis B	Placebo	228	0% at wk 48	4% at wk 48

* Integrated safety dataset of studies 437 and 438 for the first 48 weeks of treatment

These data confirm that the incidence of serum creatinine increase ≥ 0.5 mg/dL from baseline and serum phosphorus < 2.0 mg/dL in patients treated with adefovir dipivoxil at these higher doses (≥ 30 mg daily) is dose dependent for adefovir dipivoxil doses ≥ 30 mg daily with the highest incidence in the 120 mg dose group. Changes in serum creatinine and serum phosphorus were rarely observed in patients with chronic hepatitis B treated with adefovir dipivoxil 10 mg daily.

As shown in Table 6-2, the estimated time to onset of unconfirmed serum creatinine and serum phosphorus abnormalities appear similar and independent of dose in patients with events for adefovir dipivoxil doses ≥ 30 mg daily. The few events for the integrated safety population during a period of observation of 48 weeks do not permit an accurate estimation of a time to onset for this population.

Table 6-2. Kaplan-Meier Estimates for Time to Onset of Renal Abnormalities (Unconfirmed Events) in Adefovir Dipivoxil HIV and Chronic Hepatitis B Studies

Study	ADV Dose (mg)	N	K-M Estimate for Time to Onset (Patients With Events)					
			Serum Creatinine ≥ 0.5 mg/dL from Baseline			Serum Phosphorus < 2.0 mg/dL		
			Q1	Median	Q3	Q1	Median	Q3
408	120	403	25	32	39	27	31	36
417	120	104	20	28	29	28	28	29
417	60	108	27	28	32	28	28	28
437	30	173	28	36	41	28	28	32

The results of the Safety Update Report are supportive of the conclusions of the integrated safety analyses at 48 weeks. For the treatment groups in these analyses, the duration of treatment were as follows:

Treatment Group	Duration of Treatment (weeks)	
	Median	Mean (± SD)
Adefovir dipivoxil 10 mg → adefovir dipivoxil 10 mg	88.1	84.5 ± 16.17
Adefovir dipivoxil 10 mg → placebo	48.4	53.4 ± 7.8
Placebo → adefovir dipivoxil 10 mg	34.6	33.8 ± 15.4
All adefovir dipivoxil 10 mg	49.0	55.0 ± 26.5

At week 96, the Kaplan-Meier estimates of unconfirmed increases in serum creatinine (≥ 0.5 mg/dL from baseline) were 4%, 4%, and 3% in the adefovir dipivoxil 10 mg → adefovir dipivoxil 10 mg, adefovir dipivoxil 10 mg → placebo, and placebo → adefovir dipivoxil 10 mg groups, respectively. Two of these abnormalities in the adefovir dipivoxil 10 mg → adefovir dipivoxil 10 mg group were confirmed by 2 consecutive laboratory assessments (see Section 6.2.3). One patient (1%) had an unconfirmed serum phosphorus < 1.5 mg/dL by week 12 of treatment in the adefovir dipivoxil 10 mg → adefovir dipivoxil 10 mg group, which was not confirmed at the next laboratory assessment.

Summary

In patients treated with adefovir dipivoxil at doses of 30 mg daily or greater who had either chronic hepatitis B (30 mg daily) or HIV infection (60 mg and 120 mg daily), nephrotoxicity was observed after long-term (> 20 weeks) exposure. The incidence of serum creatinine increase ≥ 0.5 mg/dL from baseline and serum phosphorus decrease < 2.0 mg/dL in patients treated with adefovir dipivoxil at these higher doses (≥ 30 mg daily) was dose dependent.

The estimated time to onset of these renal laboratory abnormalities was similar in patients with these events across the range of doses.

In the integrated safety population of patients with chronic hepatitis B, 1% of patients treated with adefovir dipivoxil 10 mg had an unconfirmed serum creatinine increase ≥ 0.5 mg/dL from baseline during 48 weeks of treatment; none of the abnormalities were confirmed by two consecutive laboratory assessments. One patient treated with adefovir dipivoxil 10 mg had a serum phosphorus decrease of < 1.5 mg/dL during 48 weeks of treatment; again this abnormality was not confirmed by two consecutive laboratory assessments. With longer term follow-up of up to 109 weeks, < 1% of patients had confirmed serum creatinine increase ≥ 0.5 mg/dL from baseline and no patients had serum phosphorus < 1.5 mg/dL by week 96.

Appendix 7. Update on the Adefovir Dipivoxil Ongoing Clinical Program

Additional studies designed to supplement the existing knowledge of adefovir dipivoxil 10 mg are either underway or planned as part of the clinical development program.

Patients who have been receiving adefovir dipivoxil 10 mg once daily in studies GS-98-437 and GS-98-438 are being enrolled in open-label long-term safety and efficacy studies of adefovir dipivoxil 10 mg for an additional three years. This will provide long-term safety and efficacy for up to 5 years for approximately 200 patients treated with adefovir dipivoxil 10 mg in patients with HBeAg+ and HBeAg- chronic hepatitis B. During the long-term extension phase, clinical and laboratory parameters will be evaluated every 3 months in order to evaluate chronic safety and efficacy. The durability of antiviral activity and emergence of resistance will also be prospectively evaluated including genotypic analysis and investigations of patients with confirmed virologic rebound.

Patients who achieved HBeAg seroconversion in a previous Gilead-sponsored trial or who experienced HBeAg loss associated with HBV DNA suppression will be eligible to enroll in study GS-01-481, a Gilead observational study designed to evaluate the post-treatment durability of HBeAg or HBsAg seroconversion or HBeAg loss in patients with chronic hepatitis B for up to 5 years.

Study GS-98-435 will continue to follow a subset of the currently enrolled patients with lamivudine-resistant chronic hepatitis B, both pre- and post-liver transplantation, to provide additional long-term efficacy and safety information. This study will also provide population pharmacokinetics information for patients with renal impairment. In addition, the study will provide information to assess the potential for drug interactions between adefovir dipivoxil 10 mg and the immunosuppressive agents, cyclosporine, and tacrolimus.

A renal dosing guidelines study (study GS-02-526) is also being planned to evaluate the efficacy and safety of adefovir dipivoxil 10 mg in chronic hepatitis B patients with lamivudine-resistant hepatitis B with varying degrees of renal impairment. The study will provide single and multiple dose pharmacokinetic data when patients are dosed according to the renal dosing guidelines generated from study GS-00-473 (a single dose pharmacokinetic study in patients with varying degrees of renal impairment). This will confirm the validity of the renal dosing guidelines in chronic hepatitis B patients with renal impairment.

Study GS-00-468 evaluated a combination regimen of adefovir dipivoxil and lamivudine in patients who have not been previously exposed to either drug. The study is a collaborative study between Gilead Sciences and GlaxoSmithKline to evaluate the efficacy and safety of 52 weeks combination treatment of lamivudine 100 mg and adefovir dipivoxil 10 mg compared with lamivudine 100 mg alone in patients with chronic hepatitis B and has enrolled 115 patients. Data from this study will be available in November 2002.

Gilead also plans to evaluate adefovir dipivoxil in pediatric patients pending agreement of the pediatric development plan and will initiate studies in the 2nd Quarter 2002. A liquid

formulation of adefovir dipivoxil will soon be available and pharmacokinetic studies will be commenced initially to identify an appropriate dose. The liquid formulation will also provide an opportunity to initiate dose adjustment rather than at present just allowing dose interval adjustments. Once a dose is identified in a phase 3 study evaluating efficacy and safety study in children aged 2–18 years will be undertaken.

Other studies currently being considered are studies in the elderly and other ethnic groups. A pregnancy registry has also been set up.

Gilead is also undertaking a number of collaborative studies to further evaluate adefovir dipivoxil 10 mg in the treatment of lamivudine-resistant chronic hepatitis B in patients with compensated and decompensated liver disease and in patients with chronic hepatitis B co-infected with HIV. Further development plans are being considered and in particular strategies for combination regimens with other nucleoside analogs and pegylated interferon-α in treatment-naive patients.

The following studies are currently ongoing or in planning;

Study GS-00-470 is also a joint study between Gilead Sciences and GlaxoSmithKline. It is a stratified, partially randomized, double blind, multicenter trial, evaluating the safety and efficacy of 60 months of combination treatment (lamivudine and adefovir dipivoxil) compared to lamivudine monotherapy for patients with chronic hepatitis B who have reached a clinical endpoint in a GlaxoSmithKline-sponsored study. Patients in Stratum A (previously treated with lamivudine 100 mg) will receive the combination of lamivudine 100 mg once daily + adefovir dipivoxil of 10 mg once daily. Patients in Stratum B (previously treated with placebo) will be randomized to either lamivudine 100 mg once daily or the combination of lamivudine 100 mg once daily + adefovir dipivoxil 10 mg once daily. The study objectives are to assess the safety, antiviral activity, and clinical benefit of the addition of adefovir dipivoxil to lamivudine therapy in patients with chronic hepatitis B who have reached a clinical endpoint and exhibit evidence of disease progression.

Study GS-00-493, conducted in collaboration with GlaxoSmithKline, evaluates adefovir dipivoxil 10 mg in combination with lamivudine in chronic HBV patients who exhibit evidence of reduced clinical and virologic response to lamivudine in patients completing study 465. It is a double blind, active-controlled, randomized, stratified, multicenter study in approximately 130 patients. The objectives of this study are to assess the efficacy and safety of 2 years of lamivudine and adefovir dipivoxil or lamivudine monotherapy in patients with chronic hepatitis B who have developed a YMDD variant hepatitis B virus and exhibit evidence of reduced clinical and virologic response to lamivudine. Decompensated patients (Stratum B) will continue to receive adefovir dipivoxil and lamivudine treatment. Compensated patients (Stratum A) will receive either lamivudine 100 mg monotherapy once daily for 52 weeks or combination treatment of lamivudine 100 mg and adefovir dipivoxil 10 mg once daily for 52 weeks. HBV DNA response is the primary efficacy endpoint with success defined as achieving an HBV DNA level equal to less than or equal to 5 $\log_{10}$ copies/mL or a 2 $\log_{10}$ copies/mL reduction from baseline level in study 465 observed at weeks 48 and 52.

Gilead Sciences is also undertaking a number of studies evaluating adefovir dipivoxil 10 mg in HIV/HBV co-infected patients. Study GS-01-486i is designed to evaluate the efficacy and safety of adefovir dipivoxil 10 mg once daily in combination with lamivudine 150 mg twice daily in HIV and decompensated HBV patients who have a hepatitis B viral load of at least 1.0×10^6 copies/mL despite 52 weeks of lamivudine therapy. The primary endpoint of this study will be HBV viral load change at week 24 compared with baseline and DAVG at week 24.

Study GS-01-485i evaluates the safety and efficacy of adefovir dipivoxil 10 mg in combination with lamivudine as compared with continued lamivudine in HIV-infected patients, compares the responses between HIV-uninfected and HIV-infected subjects, and obtains specimens for studies of immune responses to HBV. HIV-infected subjects will receive lamivudine 150 mg twice daily plus adefovir 10 mg once daily (or placebo) and HIV-uninfected subjects will receive lamivudine 100 mg daily plus adefovir dipivoxil 10 mg once daily. The primary endpoint will be a comparison of the absolute HBV viral load at week 48 between the placebo and adefovir dipivoxil HIV-positive patient groups, and, for the HIV-negative population, the comparison of absolute HBV viral load at week 48 compared with baseline.

Studies GS-98-465 and its follow on study GS-98-468 will continue to collect data in patients with lamivudine-resistant chronic HBV with compensated and decompensated liver disease treated with adefovir dipivoxil in combination with lamivudine versus lamivudine treatment alone.

Combination studies with lamivudine or emtricitabine with adefovir dipivoxil 10 mg are also being conducted in chronic hepatitis B patients. Study GS-01-494i will assess the safety, antiviral activity, and clinical benefit of the combination lamivudine 100 mg once daily and adefovir dipivoxil 10 mg once daily for up to five years. The primary endpoint in this study will be a maintained combined response of virological, biochemical, and histological response at year 1 and year 4. Study GS-01-495i will evaluate the safety and efficacy of the combination of emtricitabine 200 mg once daily and adefovir dipivoxil 10 mg once daily in chronic HBV patients by assessing HBV DNA change from baseline and the proportion of patients whose HBV DNA levels are below the limit of detection.

ACTG 5127 is designed to evaluate the HBV antiviral activity of adefovir dipivoxil 10 mg compared with tenofovir disoproxil fumarate (TDF) in combination with lamivudine in chronic HIV/HBV-coinfected subjects whose HBV infection is clinically resistant to lamivudine. Subjects will be randomized in a 1:1 ratio to either adefovir dipivoxil 10 mg once daily with TDF placebo once daily or TDF 300 mg once daily with adefovir dipivoxil placebo. Subjects will receive study treatment up to 96 weeks and will be followed for an additional 16 weeks until week 112.

Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
PHASE 1/ PHASE 2											
GS-96-412 Extension, Maintenance and Follow up (f/u)	Enrollment Began September 98 Enrollment Completed	US, CA, UK	Provide drug for eligible patients who completed initial study phase of studies 412 and 413	Open Label	30 mg ADV (250 mg Carnitine as needed) or dose reduced to 10 mg ADV All patients dose reduced to 10 mg ADV	39/90 0 Extension 18 Maintenance 5 Completed 16 Discontinued	Chronic hepatitis B	N/A	Detectable by Chiron bDNA (>750,000 copies/mL)	Extension Phase: 52 weeks then 24 weeks f/u or enroll in Maintenance. Maintenance Phase: Indefinite Tx 24 weeks f/u	HBV DNA Suppression HBV Serologic Markers Liver enzymes Safety.

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
PHASE 3											
GS-98-437	Enrollment Completed LPI: March 7, 2000 First Patient Screened: 2 March 1999 First Patient Randomized: 16 March 1999 (79 Sites) End of Blinded Phase 23 July 2001	US, UK Canada Australia Germany Italy France Spain Singapore Thailand Taiwan Malaysia Philippines	Registration Study	Randomized Double Blind Placebo-Controlled	30 mg ADV + 250 mg L-Carnitine 10 mg ADV + 250 mg L-Carnitine 10 mg ADV + Plb L-Carnitine Placebo ADV+ Plb L-Carnitine Placebo ADV+ 250 mg L-Carnitine	515/500 78 discontinued	HBeAg $^{+}$ patients with chronic hepatitis B and elevated ALT	1.2 – 10 x ULN on two occasions before study entry	$\geq 1x10^{6}$ copies/mL (Roche Amplicor PCR assay < 400 copies /mL)	24 Months Treatment + Six Months Post Treatment Follow-up. Amendment 4 offers ongoing open-label ADV 10 mg. Any patient electing to discontinue will complete 16 weeks off treatment follow-up.	Primary Liver Histology Secondary HBV DNA Suppression, Serologic Markers, Liver enzymes safety.

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Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002) (Continued)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
GS-98-437 cccDNA Substudy	Enrollment-screening stopped Regulatory Submissions have been done.	Australia, France (9 Sites confirmed 6 Sites pending)	Substudy	Randomized Double Blind Placebo-Controlled	Same as 437	30	Same as 437	Same as 437	Same as 437	Same as 437	PCR quantitation of HBV cccDNA in liver biopsy samples.
GS-98-437 T Cell Substudy	Enrollment Completed (6 sites) Completed	UK, France, Italy, Germany	Substudy	Randomized Double Blind Placebo-Controlled	Same as 437	Y1 = 22 Y2 = 2	Same as 437	Same as 437	Same as 437	Same as 437	T Cell Responses.
GS-98-438	Enrollment Completed First Patient Randomized 10 January 2000	Europe Asia Australia Canada Israel Greece	Non-IND Registration Study	Randomized Double Blind Placebo-Controlled	10 mg ADV Placebo (2:1 ratio)	185/180	Chronic hepatitis B (pre-core mutant) Anti-HBe^{+}/HBV DNA^{+}	1.5 – 15 x ULN on one occasion within 12 weeks of study entry	$\geq 1x10^{5}$ copies/mL (Roche Amplicor PCR assay LLQ < 400 copies/mL) on one occasion within 12 weeks of study entry	24 months – Treatment plus 16 weeks f/u Amendment 2 offers an additional 3 years of open-label ADV 10 mg for all patients randomized to ADV 10 mg in Year 2 of original protocol	HBV DNA Suppression, Liver Histology Serologic Markers, Liver enzymes safety.
GS-98-438 cccDNA Substudy		Australia (3) France (4)	Substudy	Randomized Double Blind Placebo-Controlled	Same as 438	25	Same as 438	Same as 438	Same as 438	Same as 438	PCR quantitation of HBV cccDNA in liver biopsy samples.

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Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002) (Continued)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
GS-00-461	Enrollment Completed	US Europe Australia Canada	Collect safety and efficacy of ADV + LAM and ADV alone in LAM resistance pts.	Double Blind Placebo-Controlled	10 mg ADV 100 mg LAM	59 3 discontinued	HBeAg+ patients with LAM resistance	≥ 1.2x ULN	≥ $1x10^6$ copies/mL	48 weeks 16 weeks f/u	Change in HBV DNA using DAVG (Week 16, 48)
Durability of Seroconversion											
GS-00-481	Q4, 2001	US, Canada, Europe, Australia, Asia	Durability of Seroconversion	Open-Label Observational	No treatment	18/100	Chronic hepatitis B who have undergone HBeAg seroconversion in a Gilead study			5 years FUp	Durability of Seroconversion
Continued Access/Early Access											
GS-00-480	Q4, 2001	US, Canada, Europe, Australia, Asia	Continued access to ADV for patients completing Gilead clinical trials of ADV for chronic hepatitis B	Open-Label	10 mg ADV	45/400	Chronic hepatitis B	N/A	N/A	Until commercial availability	Long term AE and SAE data

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Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002) (Continued)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
GS-98-435	Active First Patient **Enrolled: 10 May 1999** Open enrollment Until commercialization	***Active:*** US Canada UK Germany Italy Australia New Zealand Netherlands Singapore Switzerland France Hong Kong Spain Sweden Austria Belgium Greece	Early Access to Adefovir for pre and post OLT pts not responding to Lamivudine	Open-Label	10 mg ADV	451/300 78 discontinued	OLT Lamivudine failure	> 1.2x ULN	> $1x10^6$ copies/mL Roche PCR while on Lamivudine	Open	HBV DNA change from BL, ALT normalization, Child Pugh Score improvements, Safety.
GS-99-451i	Enrollment Completed	US, Canada, Singapore, Australia, Italy	Compassionate use Adefovir for LAM Resistance chronic Hepatitis B	Open Label Named Patient Study	30 mg ADV 10 mg ADV 5 mg ADV	26/26 6 Active. 10 rolled into 435. 2 lost to follow up. 8 died.	LAM resistance chronic hepatitis B, Elevated HBV DNA Abnormal LFTS	N/A	N/A	Open	SAEs
GS-01-510	Active	France	Early access (ATU program)	Open Label	10 mg ADV	416/1000 7 discontinued	Chronic hepatitis B, Lam. Failure	> 1.2x ULN	>$1x10^6$ copies/mL Roche PCR while on Lamivudine	Until commercial availability	ADR, SAE data
GS-01-550	Q1/2002	US, Canada, Germany, Italy, Greece	Early access	Open Label	10 mg ADV	6/2000	Chronic hepatitis B Lam. Failure	> 1.2x ULN	>$1x10^6$ copies/mL Roche PCR while on Lamivudine	Until commercial availability	AE, SAEs

Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002) (Continued)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
GS-01-553	Q1/2002	UK	Early access	Named patient	10 mg ADV	4/100	Chronic hepatitis B Lam. resistance	> 1.2 x ULN	$>1x10^6$ copies/mL Roche PCR while on LAM	Until commercial availability	SAEs
GS-01-551	Q1/2002	Spain	Early access	Named patient	10 mg ADV	21/100	Chronic hepatitis B Lam. resistance	> 1.2 x ULN	$>1x10^6$ copies/mL Roche PCR while on LAM	Until commercial availability	SAEs
GS-01-552	Q1/2002	Portugal	Early access	Named patient	10 mg ADV	0/50	Chronic hepatitis B Lam. resistance	> 1.2 x ULN	$>1x10^6$ copies/mL Roche PCR while on LAM	Until commercial availability	SAEs
GS-01-554	Q1/2002	Australia	Early access (SAS program)	Named patient	10 mg ADV	6/50	Chronic hepatitis B Lam. resistance	> 1.2 x ULN	$>1x10^6$ copies/mL Roche PCR while on LAM	Until commercial availability	SAEs
GSK Collaborative Studies											
GS-99-465 (NUC20904)	Enrollment Completed	US, Canada Europe, Asia	Assess safety and efficacy of LAM and ADV in YMDD mutant Pts. compared with LAM alone.	Double-Blind Placebo Controlled Cohort A Open-label Cohort B	10 mg ADV + 100 mg LAM vs. 100 mg LAM	Cohort A: 95 Cohort B: 40 (135/130)	LAM resistance HBeAg+ / HBeAg- patients	> 1.3 x ULN	$> 1x10^6$ copies/mL	52 wks	Change in HBV DNA from Baseline.
GS-01-493 (NUC 20917)	Follow-on for 20904	US, Canada Europe, Asia	Assess safety and efficacy of LAM and ADV in YMDD mutant Pts. compared with LAM alone.	Double-Blind Placebo Controlled Cohort A Open-label Cohort B	10 mg ADV + 100 mg LAM vs. 100 mg LAM	Cohort A: 59 Cohort B: 32 (91/130)	LAM resistance HBeAg+ / HBeAg- patients	> 1.3 x ULN	$> 1x10^6$ copies/mL	52 wks	Change in HBV DNA from Baseline.

Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002) (Continued)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
GS-99-468 (NUC20912)	Enrollment Completed		Assess antiviral activity of LAM at 16 weeks versus antiviral activity of LAM + ADV at 16 weeks	Double-Blind Placebo Controlled	10 mg ADV + 100 mg LAM vs.100 mg LAM	115/100 FPI: Q1 2001 LPI	Chronic hepatitis B patients with compensated liver disease	> 1.3 x ULN	≥ 1x 10^6 copies/mL	52 wks 6 monthly Post-treatment assessments. Study being extended 1 more year To evaluate 24 months treatment.	Virologic response at week 16 using $DAVG_{16}$
GS-00-470 (NUC40021)	**Q4, 2001**	Asia Pacific	Clinical Endpoint study. Patients from NUC 4006.	Double-Blind	10 mg ADV + 100 mg LAM vs.100 mg LAM	8/600	Chronic hepatitis B patients who reached Clinical Endpoints in NUC 4006	N/A	N/A	5 yrs	Proportions of patients who reached Clinical Endpoints or ≥ 2 point increase in Child-Pugh score.
Collaborative Study Groups											
GS-00-484 (ACTG A5127)	Q2, 2002	*US Multi-Center*	Assess safety and efficacy of ADV + LAM vs TDF + LAM	Phase 2 Double-Blind Placebo Controlled	10 mg ADV vs. TDF 300 mg	0/109	Co-Infected HIV/HBV patients with LAM resistance	≤ 10x ULN	≥ 1x10^6 copies/mL	96 wks 16 wks f/u	Reduction of HBV DNA from Baseline
GS-01-495 (Triangle)	Q1, 2002	*HK*	Assess combination therapy w/emtricitabine and ADV vs. ADV alone for chronic hep B.	Randomized	10 mg ADV + 200 mg emtricitabine vs. 10 mg ADV + emtricitabine Placebo	0/30	Chronic hepatitis B, treatment naive	≥ 1.3 to < 10 xULN	≥ 1x10^6 copies/mL	48 wks	Safety, Efficacy, Viral Load.
Investigator Initiated Studies											
GS-99-460i	Enrollment Completed	Paris, France	Investigator study	Open-Label	10 mg ADV 150 mg LAM	35/35	HIV/HBV co-infected patients with LAM resistance		≥ 1x10^6 copies/mL	52 wks 24 wks f/u	Reduction of HBV DNA from Baseline.

Ongoing Clinical Studies of Adefovir Dipivoxil for Patients with Chronic Hepatitis B (as of July 2002) (Continued)

Study Phase/ Clinical Trial	Status	Location	Purpose	Design	Dose	Enrolled/ Target	Patient Population	Entry ALT	HBV DNA	Duration of Trial	Major Endpoints
GS-00-485i	Q3, 2001	NIH	Pilot Study	Randomized	10 mg ADV + 150 mg LAM vs Placebo+100 mg LAM	5/60	Co-Infected HIV/HBV	1.2 ≤ ALT ≤ 7 x ULN	≥ $1x10^6$ copies/mL	48 wks	Safety, Efficacy, Viral Load.
GS-00-486i	Q3, 2001	NIH	Pilot Study	Open-Label	10 mg ADV + 150 mg LAM	3/30	Co-Infected HIV/HBV	≤ 7x ULN	≥ $1x10^6$ copies/mL	48 wks	Safety, Efficacy, Viral Load.
GS-01-494i	Q4, 2001	US	Combination therapy with LAM + ADV for treatment of chronic hep B.	Open-Label	10 mg ADV 100 mg LAM	0/20	Chronic hepatitis B patients who are treatment naïve.	> 2 x ULN	>$1.6 x10^5$ copies/mL	5 yrs	Safety, Efficacy, Viral Load.
Pharmacokinetic Studies											
GS-00-472 Phase 1/Phase 2	Enrollment Completed	US France	PK/Viral Dynamics Single and multi dose	48 wks Open Label (7 day PK Phase)	10 mg ADV	14/12	Chronic hepatitis B, Nucleoside naive	≥ 1.2 to ≤ 10 x ULN	≥ $1x10^6$ copies/mL (Roche PCR)	48 wks treatment	PK & HBV viral dynamics and change in HBV DNA.