CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-449

MEDICAL REVIEW

Medical Officer's Review of New Drug Application
NDA # 21-449

Drug: Adefovir dipivoxil

Proposed Indication: Treatment of chronic hepatitis B in adults

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table of Content

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

1. - Materials Utilized in Review

The clinical data submitted by the applicant, Gilead Sciences, Inc., for FDA review of adefovir dipivoxil (hereinafter, "adefovir" or "ADV") for the treatment of chronic hepatitis B consisted of 102 volumes (volumes 87 to 189) in the original New Drug Application (NDA) of March 20, 2002. The clinical data cutoff date of this submission was December 31, 2001.

Subsequently, the applicant submitted a number of Responses to Request for Information and a safety update on June 7, 2002, which consists of an additional 17 volumes. The safety update contained clinical data up to February 28, 2001.

2. Background

2.1. Indication

The applicant proposes the following indication for adefovir:

Currently, two drugs, lamivudine (Epivir-HBV®) and interferon alfa-2b, recombinant (Intron® A), have been approved by the FDA for the treatment of chronic hepatitis B.

Reviewer's Comments

1. *The diagnostic criteria for chronic hepatitis B at the National Institutes of Health workshop on Management of Hepatitis B 2000 (Lok AS, Heathcote EJ, Hoofnagle JH. Management of Hepatitis B: 2000-Summary of a Workshop. Gastroenterology 2001; 120: 1828-1853) are as follows:*

   - *HBsAg positive > 6 months*
   - *Serum HBV DNA > 10^5 copies/mL*
   - *Persistent or intermittent elevation in ALT/AST levels*
   - *Liver biopsy showing chronic hepatitis (necroinflammatory score 4)*

   The last criterion, i.e., liver biopsy to assess the degree of inflammation, is optional.

2.2. Administrative History

The applicant submitted an Investigational New Drug Application (IND # ——') for adefovir for the treatment of chronic hepatitis B to the Division of Antiviral Drug Products (DAVDP) on December 17, 1996. The original IND submission included data from clinical study GS-94-404 conducted in the United Kingdom. Subsequently, the applicant conducted two phase1/phase 2 clinical studies (GS-96-412, GS-96-413), three controlled clinical phase 3 studies (registration studies GS-98-437 and GS-98-438, and study GS-00-461), an open-label clinical study (GS-98-435), and five pharmacokinetic studies (GS-00-427, GS-00-473, GS-00-474, GS-00-475, and GS-00-476). While study GS-98-438 is not formally conducted under IND # —— the original study protocol and subsequent protocol amendments were submitted to the IND. Study GS-00-461 was submitted as part of a Request for Special protocol Assessment on August 11, 2001. Additionally, the applicant has also initiated studies to evaluate long-term (3 to 5 years) safety, effectiveness, and resistance studies in subsets of patients from studies GS-98-437 and GS-98-438 (GS-00-481).

In addition to multiple teleconferences, the applicant and DAVDP also held an end-of-phase 2 meeting on April 25, 2000, and a pre-NDA meeting on August 10, 2001.

It should be noted that adefovir at significantly higher doses than those studied for chronic hepatitis B had been studied under IND # —— (submitted to DAVDP on December 20, 1994) for the treatment of human immunodeficiency virus (HIV) infection. The applicant submitted an NDA for this indication on June 28, 1999. The FDA Antiviral Drug Advisory Committee recommended against approval of the drug for the treatment of HIV infection over the concern of treatment-associated nephrotoxicity.

2.3. Proposed Labeling

The applicant proposes that the following information be included in the label:

- The recommended dose of adefovir is 10 mg daily taken orally with or without food and the optimal duration of treatment is presently unknown.

- Dosing of the drug must be adjusted for renally impaired patients. Due to the potential drug-associated nephrotoxicity, consideration should be given to monitoring for serum creatinine and phosphorus in patients "at risk or with a history of renal dysfunction."

- Patients should also be monitored for ———— after cessation of adefovir since post-treatment exacerbation of hepatitis has been observed.

- The drug should be used cautiously in geriatric population since older patients may have pre-existing renal dysfunction due to greater frequency of underlying illnesses and concomitant therapy that may potentially be nephrotoxic.

- Finally, safety and effectiveness of adefovir in pediatric patients have not been established.

2.4. Foreign Marketing

Adefovir has not been marketed in any country.

3. Chemistry, Manufacturing, and Controls

There are no identifiable Chemistry, Manufacturing, and Controls (CMC) problems with adefovir that are relevant to this clinical review. Please see review by Dr. Ko-yu Lo for additional information.

4. Animal Pharmacology

Adefovir is an oral prodrug of adefovir, a phosphonate nucleotide analog of adenosine monophosphate. *In vivo*, the drug is converted to the parent compound, adefovir, and through two phosphorylation reactions by host enzymes to adefovir diphosphate, the active metabolite that inhibits DNA polymerase. The drug has been demonstrated to have antiviral activity against a number of viruses including woodchuck hepatitis virus and human hepatitis B virus (HBV). Please see review by Dr. Lalji for additional information on virologic activity of adefovir.

Results of *in vitro* experiments have shown that adefovir can induce renal proximal tubular toxicity. Interference with the function of renal organic anion transporter 1, a protein localized in the basolateral membrane of the renal proximal tubule epithelium, has been implicated as the etiology. Adefovir-associated nephrotoxicity characterized by renal tubular nephropathology (karyomegaly, cytomegaly, tubular dilation, degeneration/regeneration, tubular epithelial cell necrosis) and elevations in creatinine and/or blood urea nitrogen (BUN), has been observed in all animal species evaluated. The incidence and severity of nephrotoxicity is related to drug dose and duration of use. In monkeys, systemic exposure of adefovir at $\geq$ 5 mg/Kg/day (i.e., approximately 3 times that achieved in humans at the recommended therapeutic dose of 10 mg daily) resulted in nephrotoxicity.

In monkey studies of adefovir, elevations in liver transaminases (2- to 3-fold) were observed at doses of $\geq$ 5 mg/Kg/day and reversible upon discontinuation of the drug.

Administration of adefovir had no effects on fertility or reproductive performance in rats. No embryotoxic or teratogenic effects were seen when pregnant rats received adefovir orally. However, intravenous administration of adefovir in pregnant rats resulted in embryotoxicity, increased incidence of fetal malformations and common variations. Fetal toxicity (decreased birth weight and crown-to-rump length) but no teratogenicity was observed in the rat developmental toxicity study and was attributed to maternal

toxicity. Developmental toxicity at doses causing maternal toxicity was also noted in the F1 generation in pre- and post-natal development study in rats.

Similar to other nucleoside analogs, adefovir has been shown to induce chromosomal aberrations (not point mutations) *in vitro* but is not genotoxic or carcinogenic in *in vivo* models. For additional information, please see review by Dr. Pritam Verma.

5. Description of Clinical Data Sources

5.1. Primary Source Data

The primary source of clinical data for this review is derived from two ongoing "pivotal" randomized, double blind, placebo-controlled clinical studies of adefovir in chronic hepatitis B patients with compensated liver disease and adequate renal function: (1) study GS-98-437 conducted in HBeAg-positive patients; and (2) study GS-98-438 in HBeAg-negative patients. Although study GS-98-438 was not formally conducted under IND # [redacted] the original study protocol and subsequent protocol amendments were submitted to the IND # [redacted] for FDA comments. Additionally, safety data from study GS-98-435, an open-label study in patients who are post-liver transplantation or waitlisted to receive liver transplant, with/without adequate renal function, and who had lamivudine-resistant HBV were also reviewed.

5.1.1. Study Type and Design

A summary of studies GS-98-437, GS-98-438, and GS-98-435 is presented in Table 5.1.1 below.

APPEARS THIS WAY
ON ORIGINAL

Table 5.1.1. Summary of Studies GS-98-437 and GS-98-438 (Primary ~~Data Source~~)

Study	Patient Population	Number of ITT Patients	Duration	Primary Endpoint
GS-98-437[1] - "Pivotal" - US and non-US study sites	- Compensated CHB, $HBeAg^+$ - ALT ≥ 1.2 x upper limit normal - Serum creatinine ≤ 1.5 mg/dL - Serum HBV DNA ≥ 10^6 copies/mL	Year 1 (48 wks): 173 (30 mg) 171 (10 mg) 167 (placebo) Year 2 (48 wks): 223 (10 mg) 212 (placebo)	96 wks	Liver biopsy at wk 48
GS-98-438[1] - "Pivotal" - No US study sites	- Compensated CHB, $HBeAg^-$ - ALT ≥ 1.5 x ULN - Serum creatinine ≤ 1.5 mg/dL - Serum HBV DNA ≥ 10^5 copies/mL	Year 1: 123 (10 mg) 61 (placebo) Year 2: 139 (10 mg) 40 (placebo)	96 wks + 3-yr extension	Liver biopsy at wk 48
GS-98-435[2]	- Lamivudine-resistant HBV - Cohort 1: adequate renal, hepatic, hematologic function at baseline - Cohort 2: inadequate renal, hepatic, hematologic function at baseline - Subcohort A: Post-liver transplant - Subcohort B: Waitlisted for liver transplant	Cohort 1A: 117 Cohort 2A: 12 Cohort 3A: 67 Cohort 1B: 46 Cohort 2B: 2 Cohort 3B: 80 ADV 10mg or 5 mg daily	Till toxicity or death	$DAVG_{24}$[3]

[1] Randomized, double blind, placebo-controlled, multicenter study.
[2] Open label, multicenter study.
[3] Time-weighted average change in serum HBV DNA from baseline at week 24.

5.1.1.1.Study GS-98-437

GS-98-437 was a randomized, double blind, placebo-controlled, multicenter study to evaluate the safety and effectiveness of adefovir 30 mg daily and adefovir 10 mg daily in the treatment of patients with, HBsAg-positive, HBeAg-positive chronic hepatitis B, serum HBV DNA ≥ 10^6 copies/mL (by experimental Roche Amplicor™ polymerase chain reaction [PCR] assay with a lower limit of quantification of 400 copies/mL) and serum alanine aminotransferase (ALT) values 1.2 to 10 times the upper limit of normal (ULN). Patients had to have compensated liver disease, adequate renal function (serum creatinine ≤ 1.5 mg/dL), and were seronegative for HIV, HCV, and HDV. Prior lamivudine, famciclovir, or IFN-α therapy was permitted provided the last dose was administered 6 months or more prior to screening or before liver biopsy was performed. Treatment with hepatotoxic, nephrotoxic drugs, or competitors of renal excretion was prohibited within 2 months prior to screening and during the study.

During the first 48 weeks of the study, patients were randomized (1:1:1) to one of the three groups: ADV 30 mg group, ADV 10 mg group, or placebo group. Since adefovir treatment may result in a decrease of serum carnitine, all patients in the ADV 30 mg group received daily administration of 250 mg of L-carnitine. Patients in the ADV 10 mg group or placebo group were randomized to receive either 250 mg of L-carnitine or L-carnitine placebo. During the second 48 weeks, patients who had received adefovir 30 mg daily received placebo once daily, patients who had received placebo received adefovir 10 mg daily, and patients who received adefovir 10 mg daily were re-randomized to receive adefovir 10 mg daily or placebo.

The doses of adefovir to be investigated in this study were based on results of study GS-96-412 (see Section 5.2). This was a phase 2, multicenter, randomized, double blind, placebo-controlled, sequential cohort, dose-escalation study of adefovir (5, 30, and 60 mg once daily) in chronic hepatitis B patients with HBeAg-positive (53 patients) and HBeAg-negative (10 patients). Treatment with adefovir resulted in statistically significant decreases in serum HBV DNA levels (by Roche Amplicor™ PCR assay) during the 12 weeks of treatment. In the HBeAg-positive patient cohort, the median serum HBV DNA change from baseline at week 12 was -0.02 $\log_{10}$ copies/mL in the placebo group, -1.82 $\log_{10}$ copies/mL in the 5 mg group, -3.78 $\log_{10}$ copies/mL in the ADV 30 mg group, and -3.34 $\log_{10}$ copies/mL in the ADV 60 mg group. After adefovir treatment was discontinued, serum HBV DNA returned to values similar to baseline levels. Six patients in the adefovir-treated groups had seroconversion by week 36 (during the 24-week off-drug follow-up period) compared to none in the placebo group. In the HBeAg-negative cohort, the median serum HBV DNA change from baseline was -3.59 $\log_{10}$ copies/mL in the ADV 30 mg group compared with -0.28 $\log_{10}$ copies/mL in the placebo group.

The study protocol was amended in June 2001 to change the primary objective to include only consideration of the ADV 10 mg group for marketing approval due to treatment-emergent nephrotoxicity seen in a number of patients in the ADV 30 mg group. Additionally, on or after September 2000, misallocation of study medication resulted in 416 of the 459 patients who entered the second 48 weeks of the study receiving at least one incorrect bottle of drug. The applicant became aware of the error on July 12, 2001. A decision was made with DAVDP concurrence to terminate the blinded phase of the study on July 19, 2001, and the study protocol was amended to offer all patients open-label treatment with adefovir 10 mg daily. Data collected during the first 48 weeks were unaffected by the error. The applicant planned to perform safety and effectiveness analyses on the second 48 weeks of the study up until the first incorrect treatment assignment.

The goal of treatment in chronic hepatitis B is to suppress viral replication and to prevent progression to cirrhosis or other long-term sequelae such as

hepatocellular carcinoma. Therefore, the applicant and DAVDP selected the primary efficacy endpoint of this study to be improvement in liver biopsy histology at week 48 compared with baseline. Liver biopsies taken at baseline (within 6 months of randomization and 6 months or more after completion of prior anti-HBV therapy) and at week 48 were evaluated for inflammation, necrosis, and fibrosis by a central pathologist using the Knodell Histology Activity Index (HAI) scoring system (*Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histologic activity in asymptomatic chronic active hepatitis. Hepatology. 1981 Sep-Oct;1(5):431-5*). The pathologist was blinded to both treatment assignment and sequence of each patient's biopsies. Histologic improvement was defined as reduction from baseline of 2 points or more in the Knodell necroinflammatory score with no concurrent worsening of Knodell fibrosis score.

The secondary endpoints of this study were: (1) change from baseline in Knodell total score, necroinflammatory score, and fibrosis score; (2) the proportion of patients with serum HBV DNA levels < 400 copies/mL at week 48 (the Roche Amplicor™ PCR assay was used for measurement of serum HBV DNA); (3) time-weighted average change from baseline up to week 48 ($DAVG_{48}$) of serum HBV DNA (log_{10} copies/mL); (4) the proportion of patients with normalization of ALT levels; (5) the proportion of patients with HBeAg seroconversion (loss of HBeAg, acquisition of anti-HBe) at week 48; and (6) the proportion of patients with HBsAg seroconversion (loss of HBsAg, acquisition of anti-HBs) at week 48.

5.1.1.2.Study GS-98-438

GS-98-438 was a randomized, double blind, placebo-controlled, multicenter study to confirm the efficacy of adefovir 10 mg daily in the treatment of patients with chronic hepatitis B, HBsAg-positive, HBeAg-negative, positive anti-HBe antibody, serum HBV DNA $\geq 10^5$ copies/mL and ALT values 1.5 to 15 times ULN. Patients had to have compensated liver disease and adequate renal function (serum creatinine $\leq$ 1.5 mg/dL), and HIV, HCV, and HDV seronegative. Prior lamivudine, famciclovir, or IFN-α therapy was permitted provided the last dose was administered 6 months or more prior to screening or before liver biopsy was performed. Treatment with hepatotoxic, nephrotoxic drugs, or competitors of renal excretion was prohibited within 2 months prior to screening and during the study.

During the first 48 weeks, patients were randomized (2:1) to receive adefovir 10 mg daily or placebo once daily. During the second 48 weeks of the study, patients who received adefovir 10 mg daily were re-randomized at the end of the first 48 weeks in a 2:1 ratio to receive adefovir 10 mg daily or placebo, and patients who had received placebo received adefovir 10 mg daily. Treatment assignment in year 2 remained blinded.

Similar to study GS-98-437, the primary efficacy endpoint of this study was improvement in liver biopsy histopathology at week 48 compared with baseline. The key secondary endpoints were: (1) change from baseline in Knodell total score, necroinflammatory score, and fibrosis score; (2) the proportion of patients with HBsAg seroconversion (loss of HBsAg, acquisition of anti-HBs) at week 48; (3) the proportion of patients with serum HBV DNA levels < 400 copies/mL at week 48; (4) time-weighted average change from baseline up to week 48 ($DAVG_{48}$) of serum HBV DNA (log_{10} copies/mL); and (5) the proportion of patients with normalization of ALT levels.

5.1.1.3.Study GS-98-435

Study GS-98-435 is an open-label study to evaluate the safety and activity of adefovir 10 mg once daily in patients post-liver transplantation or waitlisted to receive liver transplant and who had lamivudine-resistant HBV. Patients were enrolled into one of three study cohorts based on their renal, hepatic, and hematologic function at baseline, and whether they had previously received open-label adefovir through a compassionate program (study GS-99-451i). Patients with adequate renal, hepatic, and hematologic function and no prior adefovir use were assigned to cohort 1. Cohort 2 included patients who were previously enrolled in study GS-99-451i [an ongoing open-label study to evaluate adefovir 5 to 10 mg daily in 26 chronic hepatitis B patients pre- or post-liver transplantation and failing anti-HBV therapies]. Patients with significant renal, hepatic, and/or hematologic dysfunction, or other significant disease that precluded their eligibility into cohort 1were assigned to cohort 3. Each of these cohorts also included patients who had previously received a liver transplant (subcohort A), and those who were waitlisted to receive a liver transplant (subcohort B). The mean duration of lamivudine treatment prior to loss of lamivudine response was 66.4 weeks for patients in subcohort A, and 65.3 weeks for patients in subcohort B.

The primary efficacy endpoint of this study was the time-weighted average change in serum HBV DNA (log_{10} copies/mL) from baseline to week 24 ($DAVG_{24}$). The applicant has submitted only limited serum HBV DNA data on various cohorts to the NDA. A brief summary of these virologic data is presented in section 7.4.2. The safety data of this study will be presented in Section 8.

5.1.2. Demographics

Study GS-98-437 enrolled patients with HBeAg-positive chronic hepatitis B and compensated liver disease. This population represents the majority of patients seen in the United States. The study was conducted at 78 sites in the United States (US), Canada, Australia, Europe (France, Germany, Italy, Spain, United Kingdom), and Asia (Taiwan, Thailand, Malaysia, Singapore, the Philippines). There were 28 study sites in the Unites States enrolling a total of 148 (29%) patients.

Study GS-98-438 enrolled patients with HBeAg-negative compensated chronic hepatitis B. This type of disease accounts for up to 30% of chronic infection worldwide and is most prevalent in the Mediterranean, Middle East, and Asia. The study was conducted at 32 study sites in Canada, Europe, Australia, and Asia. There was no US site.

Study GS-98-435 enrolled 367 patients (as of NDA data cutoff date) either status post liver transplantation or waitlisted for liver transplantation who had lamivudine-resistant HBV. The study was conducted at 85 study sites in Canada, Europe, Australia, New Zealand, Singapore, and the United States. There were 28 sites in the United States enrolling 112 patients: 93 men (83%); 19 women (17%). Of these, 72 patients (64%) were classified as "White," 36 (32%) as "Asian," two (2%) as "Black," and two as "Other."

The demographic characteristics of patient populations in studies GS-98-437, GS-98-438, and GS-435 are summarized in Tables 5.1.2A, 5.1.2B, 5.1.2C, and 5.1.2D, respectively. The treatment groups of studies GS-98-437 and GS-98-438 were balanced demographically.

APPEARS THIS WAY
ON ORIGINAL

Table 5.1.2A. Patient Demographics in Study GS-98-437 [redacted]

Characteristic	Treatment Group			
	ADV 30 mg	ADV 10 mg	Placebo	Total
Number of randomized patients	173	172	170	515
Number of ITT patients[1]	173	171	167	511
Region				
United States	50 (29%)	50 (29%)	48 (28%)	148 (29%)
Canada	14 (8%)	14 (8%)	14 (8%)	42 (8%)
Europe	45 (26%)	46 (27%)	45 (26%)	136 (26%)
Asia	43 (25%)	42 (24%)	42 (24%)	127 (25%)
Australia	21 (12%)	20 (12%)	21 (12%)	62 (12%)
Age (yrs)				
Mean ± SD	34 ± 10.8	34 ± 11.2	37 ± 11.8	35 ± 11.3
Median	32	32	35	33
Q1, Q3	26, 41	25, 42	28, 43	26, 43
Range	17 to 68	16 to 65	16 to 66	16 to 68
Gender				
Male, n (%)	129 (75%)	130 (76%)	119 (71%)	378 (74%)
Female, n (%)	44 (25%)	41 (24%)	48 (29%)	133 (26%)
Race				
Caucasian, n (%)	64 (37%)	60 (35%)	60 (36%)	184 (36%)
Black, n (%)	5 (3%)	8 (5%)	3 (2%)	16 (3%)
Asian, n (%)	101 (58%)	102 (60%)	101 (60%)	304 (59%)
Other	3 (2%)	1 (< 1%)	3 (2%)	7 (1%)
Prior HBV treatment				
Interferon-α	46 (27%)	42 (25%)	35 (21%)	123 (24%)
Lamivudine	6 (3%)	1 (< 1%)	3 (2%)	10 (2%)
Other	11 (6%)	7 (4%)	9 (5%)	27 (5%)

[1]ITT: Intent-to-treat (received at least one dose of study drug)
(Source: NDA 21-449, Volume 112, Table 6)

APPEARS THIS WAY
ON ORIGINAL

Table 5.1.2B. Patient Demographics in Study GS-98-438

Characteristic	Treatment Group		
	ADV 10 mg	Placebo	Total
Number of randomized patients	123	62	185
Number of ITT patients	123	61	184
Region			
Canada	17 (14%)	8 (13%)	25 (14%)
Europe	78 (63%)	39 (63%)	117 (63%)
Asia	15 (12%)	8 (13%)	23 (12%)
Australia	13 (11%)	7 (11%)	20 (11%)
Age (yrs)			
Mean ± SD	46 ± 9.8	45 ± 10.4	46 ± 10
Median	46	45	46
Q1, Q3	40, 53	39, 53	39, 53
Range	18 to 65	22 to 65	18 to 65
Gender			
Male	102 (83%)	50 (82%)	152 (83%)
Female	21 (17%)	11 (18%)	32 (17%)
Race			
Caucasian	82 (67%)	40 (66%)	122 (66%)
Black	5 (4%)	1 (2%)	6 (3%)
Asian	36 (29%)	20 (33%)	56 (30%)
Other	0 (0%)	0 (0%)	0 (0%)
Prior HBV treatment			
Interferon-α	48 (39%)	28 (46%)	76 (41%)
Lamivudine	10 (8%)	4 (7%)	14 (8%)
Other	7 (6%)	7 (11%)	14 (8%)

(Source: NDA 21-449, Volume 146, Table 9)

APPEARS THIS WAY
ON ORIGINAL

Table 5.1.2C. Patient Demographics of Cohorts 1A, 2A, and 3A (Post-Liver Transplantation) in Study GS-98-435

	Patient Cohort			Total
	1A	2A	3A	
Number of patients	117	12	67	196
Age (yrs)				
Mean ± SD	51.9 ± 10.4	50.3 ± 10.9	53.5 ± 11.8	52.4 ± 10.9
Median	53.0	52.0	55.0	54.0
Q1, Q3	45, 60	47, 58	45, 63	45, 61
Range	12, 71	23, 61	19, 75	12, 75
Gender				
Male, n (%)	95 (81%)	12 (100%)	55 (82%)	162 (83%)
Female, n (%)	22 (19%)	0	12 (18%)	34 (17%)
Race				
Caucasian	90 (77%)	9 (75%)	55 (82%)	154 (79%)
Black	1 (1%)	0	0	1 (1%)
Asian	26 (22%)	3(25%)	12 (18%)	41 (21%)
Other	0	0	0	0
HBV DNA (log_{10})				
Mean ± SD	8.1 ± 1.1	4.0 ± 1.3	7.9 ± 1.5	7.8 ± 1.6
Median	8.3	3.8	8.3	8.2
Q1, Q3	7.7, 8.8	2.6, 5.2	7.6, 8.9	7.5, 8.8
Range		[redacted]		
Child-Pugh score[1]				
5-6 (Class A)	57 (88%)	6 (100%)	29 (59%)	92 (77%)
7-9 (Class B)	8 (12%)	0	17 (35%)	25 (21%)
10-15 (class C)	0	0	3 (6%)	3 (3%)
HBeAg				
Positive	61 (68%)	5 (50%)	37 (74%)	103 (69%)
Negative	29 (32%)	5 (50%)	13 (26%)	47 (31%)
ALT				
Mean ± SD	122 ± 103	56 ± 29	146 ± 207	126 ± 146
Median	85	62	85	83
Q1, Q3	57, 140	31, 79	42, 148	53, 133
Range		[redacted]		
Prior HBIG therapy	6 (33%)	4 (40%)	14 (33%)	44 (34%)

[1] Child-Pugh score (for evaluating prognosis in cirrhosis) class A: life expectancy 15 to 20 years; class B: indicated for liver transplantation; class C: life expectancy 1 to 3 years. (Source: NDA 21-449, Volume 159, Listing 4)

Table 5.1.2D. Patient demographics of Cohorts 1B, 2B, and 3B (Waitlisted for Liver Transplantation) in Study GS-98-435

	Patient Cohort			Total
	1B	2B	3B	
Number of patients	46	2	80	128
Age (yrs)				
Mean ± SD	49.4 ± 12.2	54.0 ± 17.0	49.3 ± 9.4	49.4 ± 10.5
Median	52.5	54.0	50.0	50.5
Q1, Q3	43, 59	42, 66	43, 55	43, 57
Range	18, 71	42, 66	18, 72	18, 72
Gender				
Male	38 (83%)	2 (100%)	70 (88%)	110 (86%)
Female	8 (17%)	0	10 (13%)	18 (14%)
Race				
Caucasian	31 (67%)	2 (100%)	48 (60%)	81 (63%)
Black	1 (2%)	0	2 (3%)	3 (2%)
Asian	13 (28%)	0	29 (36%0	42(33%)
Other	1 (2%)	0	1 (1%)	2 (2%)
HBV DNA (log_{10})				
Mean ± SD	7.2 ± 1.3	5.2 ± 3.0	7.1 ± 1.6	7.1± 1.5
Median	7.5	5.2	7.4	7.4
Q1, Q3	6.6, 8.1	3.1, 7.3	6.5, 8.1	6.6, 8.1
Range				
Child-Pugh score[1]				
5-6 (Class A)	12 (52%)	1 (100%)	12 (28%)	25 (37%)
7-9 (Class B)	9 (39%)	0	17 (40%)	26 (39%)
10-15 (class C)	2 (9%)	0	14 (33%)	16 (24%)
HBeAg				
Positive	11 (28%)	2 (100%)	32 (52%)	45 (44%)
Negative	29 (73%)	0	29 (48%)	58 (56%)
ALT				
Mean ± SD	188 ± 256	75 ± 57	121 ± 137	146 ± 193
Median	85	75	69	75
Q1, Q3	61, 160	35, 116	45, 129	49, 158
Range				

[1] Child-Pugh score (for evaluating prognosis in cirrhosis) class A: life expectancy 15 to 20 years; class B: indicated for liver transplantation; class C: life expectancy 1 to 3 years. (Source: NDA 21-449, Volume 159, Listing 4)

Reviewer's Comment

African American, Hispanic American, and American Indian/Alaska Native populations were underrepresented in studies GS-98-437 and GS-98-435 (studies enrolling patients in the United States). The applicant should make a diligent attempt to enroll more of these patients in future clinical studies with adefovir.

5.2. Secondary Source Data

Additional safety and efficacy data, albeit limited, were also available at the time of this NDA submission for the following clinical studies:

- Three dose-ranging studies (GS-94-404, GS-96-412, and GS-96-413) in patients with chronic hepatitis B.
- An active-controlled clinical study of adefovir alone, lamivudine alone, and adefovir plus lamivudine in chronic hepatitis B patients with lamivudine resistant (YMDD mutant) HBV (study GS-00-461).
- A randomized, double blind, placebo-controlled (stratum A) and open-label (stratum B) study co-sponsored with GlaxoSmithKline (study GS-99-465) evaluating the addition of adefovir to lamivudine therapy in patients with chronic hepatitis B and lamivudine resistant (YMDD mutant) HBV.
- An investigator-sponsored open-label study in chronic hepatitis B patients co-infected with HIV and compensated liver disease (study GS-99-460i).
- One open-label compassionate use study in patients with chronic hepatitis B and end-stage liver disease and lamivudine resistant HBV (study GS-99-451i).

Brief summaries of results of these studies are provided below.

5.2.1. Study GS-94-404

GS-94-404 was a randomized, double blind, placebo-controlled, dose-escalating study of adefovir 125, 250, and 500 mg once daily in patients with chronic hepatitis B, HBeAg-positive, and elevated ALT levels. However, safety data emerging from the HIV development program and adequate evidence of antiviral activity at 125 mg (the first of the escalating dose levels) resulted in cancellation of the planned escalation of doses beyond 125 mg. Twenty male patients (13 co-infected with HIV) were randomized to receive adefovir 125 mg daily (15 patients) and placebo (5 patients) for 4 weeks. At the 4-week assessment, serum HBV DNA levels (measured by Digene Hybrid Capture® assay) had changed by a mean of -3.99 $\log_{10}$ pg/mL and 0.001 $\log_{10}$ pg/mL for ADV 125 mg group and placebo group, respectively. Subsequently, 15 patients were maintained on adefovir treatment: 8 patients in the 120 mg group and 7 in the 60 mg group for 24 weeks. During treatment, no difference in response was observed between the two cohorts. Serum HBV DNA levels were reduced by a mean of 3.02 $\log_{10}$ mEq/mL (Chiron Quantiplex™ bDNA assay). After study medication was discontinued, serum HBV DNA returned to baseline levels. No patients experienced HBeAg seroconversion.

5.2.2. Study GS-96-412 [redacted]

GS-96-412 was a phase 2, multicenter (10 sites in the US, Canada, UK, and Australia), randomized, double blind, placebo-controlled, sequential cohort, dose-escalation study of adefovir (5, 30, and 60 mg once daily) in chronic hepatitis B patients with HBeAg-positive (53 patients) and HBeAg-negative (10 patients). Patients were randomized to receive either adefovir (15 patients in the 60 mg, 23 in the 30 mg groups, and 9 in the 5 mg group) or placebo (16 patients) for 12 weeks followed by a 24-week off-drug follow-up period. Subsequently, patients were treated with adefovir 30 mg daily in an open-label extension phase for a median period of 40 weeks. In May 2000, the applicant's data monitoring committee determined that the adefovir 30 mg daily dose was not suitable for long-term dosing following the emergence of nephrotoxicity after 20 or more weeks of therapy. As a result, the adefovir dose was reduced to 10 mg daily by protocol amendment.

Treatment with adefovir resulted in statistically significant decreases in serum HBV DNA levels (by Roche Amplicor™ PCR assay) during the 12 weeks of treatment. In the HBeAg-positive patient cohort, the median serum HBV DNA change from baseline at week 12 was -0.02 $\log_{10}$ copies/mL in the placebo group, -1.82 $\log_{10}$ copies/mL in the 5 mg group, -3.78 $\log_{10}$ copies/mL in the ADV 30 mg group, and -3.34 $\log_{10}$ copies/mL in the ADV 60 mg group. After adefovir treatment was discontinued, serum HBV DNA returned to values similar to baseline levels. Six patients in the adefovir groups had seroconversion by week 36 (during the 24-week off-drug follow-up period) compared to none in the placebo group. In the HBeAg-negative cohort, the median serum HBV DNA change from baseline was -3.59 $\log_{10}$ copies/mL in the ADV 30 mg group compared with -0.28 $\log_{10}$ copies/mL in the placebo group.

5.2.3. Study GS-96-413

This was a placebo-controlled, sequential dose escalation study to evaluate adefovir 30, 60, or 120 mg once daily for 12 weeks in patients with chronic hepatitis B, HBeAg-positive. The study design was identical to that of study GS-96-412, except that patients were required to have ALT < 1.2 x ULN at baseline. Based on results of an interim analysis showing anti-HBV activity in these patients, enrollment into the study was stopped at 15 patients, with 12 in the ADV 30 mg group and 3 in the placebo group. Treatment with adefovir 30 mg daily resulted in a median change of serum HBV DNA of -2.83 $\log_{10}$ copies/mL compared with -0.03 $\log_{10}$ copies/mL in the placebo group. Serum HBV DNA returned to baseline values after adefovir treatment was discontinued.

5.2.4. Study GS-00-461

GS-00-461 is an ongoing randomized, active-controlled study evaluating the safety and activity of adefovir 10 mg once daily with or without lamivudine in patients with chronic hepatitis B who have developed lamivudine-resistant (YMDD mutant) HBV. The study duration is 48 weeks with a primary efficacy endpoint of time-weighted average change from baseline of serum HBV DNA up to week 16 ($DAVG_{16}$). Patients with compensated liver disease, adequate renal functions, and elevated ALT were enrolled and randomized in a 1:1:1 ratio to receive adefovir 10 mg monotherapy (20 patients), lamivudine 100 mg daily monotherapy (19 patients), or combination therapy with adefovir 10 mg daily plus lamivudine 100 mg daily (20 patients). Fifty-eight patients (60% Caucasian, 36% Asian) completed at least 16 weeks of treatment. Treatment with adefovir 10 mg daily alone or in combination with lamivudine 100 mg daily resulted in similar median $DAVG_{16}$ change (log_{10} copies/mL) of -2.46 and -2.45, respectively, compared with -0.07 in the lamivudine monotherapy group. A greater proportion of patients in the ADV 10 mg group (32%) and combined adefovir plus lamivudine groups (42%) had normalization of ALT compared with lamivudine monotherapy (6%).

5.2.5. Study GS-99-460i

GS-99-460i is an open-label investigator-initiated (single center) study to evaluate the safety and activity of adefovir 10 mg daily in patients with lamivudine-resistant chronic hepatitis B who were co-infected with HIV. Adefovir 10 mg once daily was added to lamivudine therapy (150 mg twice daily as part of antiretroviral regimen). Thirty-five patients with confirmed M522V or M552I (YMDD) mutations of the HBV DNA polymerase gene were enrolled. At the time of this reporting, the median time on adefovir was 72 weeks (range 68 to 72 weeks).

Serum HBV DNA changes from baseline (log_{10} copies/mL) at weeks 24, 48 and 72 were -3.40, -4.07, and -4.77, respectively. Twenty-five percent of patients had ALT normalization at week 72. In a subset of 14 patients with liver biopsy data, median liver necroinflammatory scores assessed by the METAVIR scoring system decreased from A2 (range 0-3) pretreatment to A1 (0-2) at week 52. Fibrosis scores also decreased from median F3 (0-4) pretreatment to F2 (0-3).

5.2.6. Study GS-99-465

GS-99-465 is an ongoing study sponsored by GlaxoSmithKline designed to evaluate the safety and activity of 52 weeks of adefovir 10 mg daily in combination with lamivudine compared with lamivudine monotherapy in chronic hepatitis B patients with YMDD-mutant HBV. Patients were stratified as follows: stratum A includes patients with HBeAg-positive compensated liver disease; stratum B includes either HBeAg-positive or HBeAg-negative patients with decompensated liver disease. Patients in stratum A were randomized to receive either adefovir 10 mg once daily or matching placebo in a double blind manner in addition to ongoing open-label lamivudine therapy (100 mg once daily). Patients in stratum B received open-label treatment with combined adefovir 10 mg daily and lamivudine 100 mg daily. At the time of this report, only data from 39 evaluable stratum B patients were available. At week 24, all patients had HBV DNA response with median serum HBV DNA change of -3.9 $\log_{10}$ copies/mL (Roche COBAS Amplicor HBV Monitor™ assay). Fifteen percent of patients achieved unquantifiable serum HBV DNA (< 200 copies/mL). Of the 29 patients who were HBeAg-positive at entry, 3 patients (10%) became HBeAg negative at week 24. Forty-nine percent of patients also had normalization of ALT.

5.3. Extent of Drug Exposure

As of February 28, 2002, a total of 2,084 subjects have been enrolled in clinical trials to evaluate adefovir (doses ranging from 5 to 125 mg/day) for the treatment of chronic hepatitis B. Based on data at the time of the NDA submission, as of December 31, 2001, a total of 523 patients with chronic hepatitis B patients have been treated for at least 48 weeks, 316 patients up to 72 weeks, and 70 patients for up to 96 weeks.

5.4. Comment on Adequacy of Clinical Experience

Since the applicant and DAVDP were in close consultation throughout the clinical development of adefovir for chronic hepatitis B, there was no important issue on the adequacy of clinical data submitted to this NDA.

5.5. Comment on Data Quality and Completeness

The applicant provided adequate and reasonably well-organized clinical data for this NDA review.

6. Human Pharmacokinetic Considerations

Please see the biopharmaceutical review by Dr. R. Kumi for relevant information.

7. Review of Efficacy Data

This section reviews the efficacy results of two confirmatory studies, GS-98-437 and GS-98-438. The primary population for analysis is the intent-to-treat (ITT) population. This includes all patients who were randomized into the study without major protocol violations and who received at least one dose of study drug. Where relevant, results of study GS-98-435 will also be presented.

7.1. Disposition of Patients

A total of 515 patients were randomized into study GS-98-437, and 185 patients into study GS-98-438. Their dispositions in the first 48 week are summarized in Table 7.1A and Table 7.1B, respectively.

Table 7.1A. Patient Disposition in the First 48 Weeks in Study GS-98-437

	Treatment Group			
	ADV 30 mg	ADV 10 mg	Placebo	Total
Total number randomized	173	172	170	515
Received at least one dose (ITT)	173	171	167	511
Received drug through 48 weeks	159 (92%)	159 (92%)	154 (92%)	472 (92%)
Discontinued prior to 48 weeks:	14 (8%)	12 (7%)	13 (8%)	39 (8%)
Adverse event	5 (3%)	4 (2%)	1 (< 1%)	10 (2%)
Withdrew consent	3 (2%)	3 (2%)	7 (4%)	13 (3%)
Lost to follow-up	1 (< 1%)	2 (1%)	1 (< 1%)	4 (<1%)
Disease progression	1 (< 1%)	0 (0%)	1 (< 1%)	2 (< 1%)
Non-compliance	2 (1%)	2 (1%)	2 (1%)	6 (1%)
Other[1]	2 (1%)	1 (< 1%)	1 (< 1%)	4 (< 1%)

[1] One patient each in the ADV 30 mg group and placebo group discontinued the study due to pregnancy; one patient each in the ADV 30 mg group and ADV 10 mg group refused to undergo week 48 liver biopsy.
(Source: NDA 21-449, Volume 112, Table 12)

Table 7.1B. Patient Disposition in the First 48 Weeks in Study GS-98-438

	Treatment Group		
	ADV 10 mg	Placebo	Total
Total number randomized	123	62	185
Received at least one dose (ITT)	123	61	184
Received drug through 48 weeks	120 (98%)	60 (98%)	180 (98%)
Discontinued prior to 48 weeks:	3 (2%)	1 (2%)	4 (2%)
Adverse event	1	0	1
Withdrew consent	1	1	2
Lost to follow-up	1	0	1

(Source: NDA 21-449, Volume 146, Table 12)

In study GS-98-437 a total of 459 patients completed the first 48 weeks of the study and were randomized to receive additional treatment in the second 48 weeks. In study GS-98-438, 180 patients completed the first 48 weeks of treatment and were re-randomized to receive further treatment for the second 48 weeks. Their dispositions are summarized in Tables 7.1C and 7.1D, respectively.

APPEARS THIS WAY
ON ORIGINAL

Table 7.1C. Patient Disposition in the Second 48 Weeks of Study GS-98-437

	Treatment Assignment				
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo	Total
Number randomized to treatment	150	85	71	153	459
Received at least one dose (ITT)	138	85	70	142	435
Discontinued (at time of report)	2 (1%)	0	1 (1%)	9 (6%)	12 (3%)
Reason for discontinuation:					
Adverse event	0	0	1 (1%)	4 (3%)	5 (1%)
Withdrew consent	0	0	0	1 (<1%)	1 (<1%)
Lost to follow-up	1 (<1%)	0	0	2 (1%)	3 (<1%)
Prohibited medication	0	0	0	1 (<1%)	1 (<1%)
Other[1]	1 (<1%)	0	0	1 (<1%)	2 (<1%)
Received incorrect drug treatment In the second 48 weeks	126 (91%)	81 (95%)	67 (96%)	119 (84%)	393 (90%)

[1] One patient in the ADV 30 mg to placebo group moved overseas; one patient in the placebo to ADV 10 mg had HIV infection.
(Source: NDA 21-449, Volume 113, Tables 2, 6, and 9)

Following the first incorrect treatment assignment in study GS-98-437, an additional 10 patients (2%) discontinued study drug for the following reasons: five (1%) due to adverse events/intercurrent illness; two each (< 1%) due to loss-to-follow-up and noncompliance; and one (< 1%) due to patient's request to discontinue the study.

Table 7.1D. Patient Disposition in the Second 48 Weeks of Study GS-98-438

	Treatment Group			
	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	Placebo to ADV 10 mg	Total
Number randomized to treatment	80	40	60	180
Received at least one dose (ITT)	79	40	60	179
Discontinued (at time of report)	0	0	0	0

(Source: NDA 21-449, Volume 147, Table 8)

7.2. Protocol Deviations

Protocol deviations of both studies GS-98-437 and GS-98-438 reported in an internal audit by [redacted] are summarized in Table 7.2.

- Table 7.2. Summary of Protocol Deviations

Type of Protocol Deviation	Number of Deviations	
	GS-98-437	GS-98-438
Any deviation	649	886
Procedural deviation	165	438
Study visit outside defined window	170	322
Inclusion/exclusion criteria	248	89
Laboratory deviation	63	30
Regulatory deviation	3	7

(Source: NDA 21-449, SN 006)

Notable are the following deviations in study GS-98-437:

- There were three "regulatory" deviations documented in study GS-98-437. These were related to obtaining informed consent. These issues were satisfactorily addressed by the investigational sites.

- The investigator at study site # 370 apparently performed off-protocol HBeAg tests using a local laboratory on five patients (two on placebo and three on adefovir treatment) after completion of the first 48 weeks of the study. These were considered major protocol violations by the medical monitor.

- Patient ID # 0381-1032 (study site # 381) had baseline biopsy performed 1 year prior to enrollment, an unacceptable deviation.

- Patient ID # 0468-6050 (study site # 468) experienced elevated ALT (20 x ULN) at month 15. Subsequently, the investigator performed off-protocol serum HBV DNA monitoring at months 15 and 20 citing "ethical" concerns even though the investigator was aware that it was a major protocol deviation to do so.

- A number of protocol deviations occurred at study site # 473 which enrolled a total of eight patients. These included missed drug doses, dispensing open-label L-carnitine by error, and multiple lapses and missing follow-up visits. It was reported that the investigator did not plan to see two patients for any follow-up visits.

Study GS-98-438 was noted for the following protocol deviations:

- One investigator (study site # 338) apparently dated five of seven patients' informed consent forms.

- One patient (ID # 0470-5509) on adefovir 10 mg daily was noted to have developed hepatocellular carcinoma at month 14 of the study. Both baseline and week 48 liver biopsies showed moderate necroinflammation and Knodell fibrosis score of 3 (non-cirrhosis).

- Serum HBV DNA tests were performed on two patients, ID # 0477-5512 (placebo group) and ID # 0477-5545 (ADV 10 mg group) at study site # 477. One test was ordered by a nurse for no apparent reason and the other by the investigator at the patient's request. These protocol violations could have potentially affected the blinded nature of the study at this site.

7.3. Baseline Disease Characteristics

Tables 7.3A and 7.3B summarize baseline disease characteristics of the intent-to-treat patient population in studies GS-98-437 and GS-98-438, respectively. All treatment groups of both studies were balanced with respect to baseline liver biopsy findings, serum HBV DNA levels, ALT levels, and history of prior therapy.

Table 7.3A. Baseline Disease Characteristics in Study GS-98-437[redacted]

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Knodell HAI scores			
Necroinflammatory score[1]			
Mean ± SD	7.84 ± 2.82	7.37 ± 2.75	7.83 ± 2.89
Median	8	7	8
Q1, Q3	7, 10	7, 9	7, 10
Fibrosis score[2]			
Mean ± SD	1.71 ± 1.06	1.64 ± 1.09	1.83 ± 1.12
Median	1	1	1
Q1, Q3	1, 3	1, 3	1, 3
Cirrhosis	7 (4%)	12 (7%)	13 (8%)
Total score			
Mean ± SD	9.55 ± 3.33	9.01 ± 3.33	9.65 ± 3.45
Median	10	9.5	10
Q1, Q3	8, 12	8, 11	8, 12
n	165 (95%)	168 (98%)	161 (96%)
HBV DNA (log_{10} copies/mL)			
Mean ± SD	8.22 ± 0.84	8.25 ± 0.90	8.12 ± 0.89
Median	8.34	8.40	8.33
Q1, Q3	7.70, 8.81	7.69, 8.87	7.50, 8.76
ALT (U/L)			
Mean ± SD	124 ± 96	139 ± 154	139 ± 131
Median	92	95	94
Q1, Q3	63, 147	65, 165	69, 159
HBeAg positive	165 (95%)	171 (100%)	161 (96%)
Prior therapy			
Interferon-α	46 (27%)	42 (25%)	35 (21%)
Lamivudine	6 (3%)	1 (< 1%)	3 (2%)
Other	11 (< 7%)	7 (< 4%)	9 (< 6%)

[1] Knodell necroinflammatory score: 0 = absence of activity; 1-3 = mild activity; 4-9 = moderate activity; 10-18 = marked activity.

[2] Knodell fibrosis score: 0 = absence of fibrosis; 1 = fibrosis restricted to the portal area; 2 = fibrosis involving periportal or rare portal-portal septa; 3 = fibrosis involving many septa leading to subjective architectural distortion; 4 = cirrhosis.

(Source: NDA 21-449, Volume 112, Table 5)

Table 7.3B. Baseline Disease Characteristics in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Knodell HAI scores		
Necroinflammatory score		
Mean ± SD	7.73 ± 2.74	7.09 ± 2.71
Median	8	7
Q1, Q3	7, 10	5, 10
Fibrosis score		
Mean ± SD	1.88 ± 1.17	1.81 ± 1.14
Median	1	1
Q1, Q3	1, 3	1, 3
Cirrhosis	14 (11%)	6 (10%)
Total score		
Mean ± SD	9.61 ± 3.31	8.89 ± 3.36
Median	10	9
Q1, Q3	8, 12	6, 11
n	121 (98%)	57 (93%)
HBV DNA (log_{10} copies/mL)		
Mean ± SD	6.92 ± 0.86	6.93 ± 0.95
Median	7.10	7.05
Q1, Q3	6.35, 7.53	6.24, 7.67
ALT (U/L)		
Mean ± SD	143 ± 125	150 ± 195
Median	93	100
Q1, Q3	69, 165	72, 161
Prior therapy		
Interferon-α	48 (39%)	28 (46%)
Lamivudine	10 (8%)	4 (7%)
Other	7 (6%)	7 (11%)

(Source: NDA 21-449, Volume 146, Table 7)

In study GS-98-437, the median serum HBV DNA was 8.36 log10 copies/mL. The median Knodell necroinflammatory score was 8 (moderate necroinflammatory activity) and the median fibrosis score was 1 (mild fibrosis confined to the portal area). Except for two patients with periportal injury score of 6, none of the patients had a score greater than 4 in any component of the Knodell scoring system. The median ALT was 2.3 times the upper limit of normal. Eleven of the 511 patients (2%) were HBeAg-positive at screening but became HBeAg-negative at baseline. Thirty-two patients (6%) had cirrhosis (Knodell fibrosis score of 4). Three percent of patients did not have baseline liver biopsy results. These latter protocol deviations do not appear to compromise data integrity.

In study GS-98-438, the median serum HBV DNA was 7.08 $\log_{10}$ copies/mL. The median Knodell necroinflammatory score was 7 (moderate necroinflammatory activity) and the median fibrosis score was 1 (mild fibrosis confined to the portal area). With the exception of one patient who had a periportal injury score of 6, none of the patients had a score greater than 4 in any component of the Knodell scoring system. The median ALT was 2.3 times the upper limit of normal. Twenty patients (11%) had cirrhosis. Three percent of patients did not have baseline liver biopsy results. These latter protocol deviations do not appear to compromise the overall data integrity.

The distribution of baseline Knodell fibrosis scores in studies GS-98-437 and GS-98-438 is summarized in Tables 7.3C and 7.3D, respectively. While the inclusion criteria limited study enrollment to patients with "compensated liver disease" (i.e., prothrombin time ≤ 1 second above normal range, albumin ≥ 3 g/dL, total bilirubin ≤ 2.5 mg/dL, no history of variceal bleeding, no history of encephalopathy), a small number of patients (6% in GS-98-437, 11% in GS-98-438) with cirrhosis (i.e., Knodell fibrosis score of 4) were also included in these studies. It was likely that these patients had early or "incomplete" cirrhosis, and thus clinical manifestations of hepatic decompensation were not apparent at the time of study enrollment.

Table 7.3C. Baseline Knodell Fibrosis Score in Study GS-98-437

	Treatment Group			
	ADV 30 mg	ADV 10 mg	Placebo	Total
Number of ITT patients	173	171	167	511
Knodell fibrosis score[1]				
0	4 (2%)	5 (3%)	2 (1%)	11 (2%)
1	104 (60%)	113 (66%)	98 (59%)	315 (62%)
3	50 (29%)	38 (22%)	48 (29%)	136 (27%)
4	7 (4%)	12 (7%)	13 (8%)	32 (6%)
Missing biopsy	3 (2%)	0 (0%)	2 (1%)	5 (<1%)
Inadequate for assessment	5 (3%)	3 (2%)	4 (2%)	12 (2%)

[1] Knodell fibrosis score: 0 = absence of fibrosis; 1 = fibrosis restricted to the portal area; 2 = fibrosis involving periportal or rare portal-portal septa; 3 = fibrosis involving many septa leading to subjective architectural distortion; 4 = cirrhosis.
(Source: NDA 21-449, Volume 112, Table 5)

Table 7.3D. Baseline Knodell Fibrosis Score in Study GS-98-438

	Treatment Group		
	ADV 10 mg	Placebo	Total
Number of ITT patients	123	61	184
Knodell fibrosis score			
0	1 (<1%)	0 (0%0	1 (<1%)
1	73 (59%)	37 (61%)	110 (60%)
3	33 (27%)	14 (23%)	47 (26%)
4	14 (11%)	6 (10%)	20 (11%)
Missing biopsy	0 (0%)	0(0%)	0 (0%)
Inadequate for assessment	2 (2%)	4 (7%)	6 (3%)

(Source: NDA 21-449, Volume 146, Table 7)

7.4. Efficacy Results

The population for efficacy evaluation will be the intent-to-treat population. According to the applicant, treatment compliance, based on study drug bottles dispensed and returned, did not appear to be a problem in studies GS-98-437 and GS-98-438.

7.4.1. Histologic Response

7.4.1.1.Primary Analysis

The histologic activity index (HAI) of Knodell is a detailed grading and staging system that has been in existence for over a decade and has been widely used in clinical trials. It has four components with higher score indicating more severe abnormalities as follows:

- periportal injury (score of 0 to 10): 0 = none; 1 = mild; 3 = moderate; 4 = marked; 5 = moderate bridging necrosis; 6 = marked bridging necrosis; 10 = multiacinar necrosis
- parenchymal injury (score of 0 to 4): 0 = none; 1 = mild; 3 = moderate; 4 = marked
- portal inflammation (score of 0 to 4): 0 = none; 1 = mild; 3 = moderate; 4 = marked
- fibrosis (score of 0 to 4): 0 = none; 1 = portal; 3 = bridging; 4 = cirrhosis

The necroinflammatory score (range 0 to 18) is the sum of the first three components: periportal injury; parenchymal injury; and portal inflammation. It reflects the degree of disease activity or the "grade" of chronic hepatitis. A score of 0 denotes absence of activity; score of 1 to 3, mild activity; score of 4 to 9, moderate activity; and score of 10 to 18, marked activity. The fibrosis score reflects the "stage" of chronic hepatitis as a result of prior inflammatory

insult. A score of 0 indicates absence of fibrosis (i.e., normal connective tissue); score of 1, fibrosis is restricted to the portal area; score of 2, fibrosis involves periportal or rare portal-portal septa; score of 3, fibrosis involves many septa leading to subjective architectural distortion; and score of 4, the presence of cirrhosis. The Knodell total score, i.e., the sum of necroinflammatory score and fibrosis score (range 0 to 22), is not useful in assessing liver biopsy since it does not discriminate grading from staging of chronic hepatitis.

In study GS-98-437, 88% of patients had evaluable baseline and week 48 liver biopsies. In study GS-98-438, the figure was 92%. The frequencies of inadequate or missing biopsies were comparable among treatment groups.

The primary efficacy endpoint of the pivotal studies was histologic improvement, defined as ≥ 2-point decrease from baseline in the Knodell necroinflammatory score with no concurrent worsening fibrosis score at week 48.

In study GS-98-437, there was a statistically significant histologic improvement at week 48 in the ADV 30 mg treatment group and ADV 10 mg treatment group compared with placebo. As shown in Table 7.4.1.1C, the histologic improvement occurred in 67% of patients in the ADV 30 mg group and 59% in the ADV 10 mg group compared to 28% in the placebo group ($p < 0.001$).

Table 7.4.1.1C. Proportions of Patients with Histologic Improvement (Inadequate/Missing Biopsies Excluded) in Study GS-98-437

	Treatment group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number of adequate biopsy pairs	147	152	149
Improvement[1]	99 (67%)	89 (59%)	41 (28%)
No improvement	48 (33%)	63 (41%)	108 (72%)
p-value[2]	< 0.001	< 0.001	

[1] Improvement defined as ≥ 2-point decrease in Knodell necroinflammatory score from baseline at week 48 with no concurrent worsening fibrosis score.
[2] Compared to placebo (Chi-Square tests)
(Source: NDA 21-449, FDA analysis)

In study GS-98-438, there was also a statistically significant histologic improvement at week 48 in the ADV 10 mg group compared with placebo. The histologic improvement occurred in 69% of patients in the ADV 10 mg group compared with 36% in the placebo group ($p < 0.001$) as shown in Table 7.4.1.1D.

Table 7.4.1.1D. Proportions of Patients with Histologic Improvement (Inadequate/Missing Biopsies Excluded) in Study GS-98-438

	Treatment group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Number of adequate biopsy pairs	113 (91%)	56 (90%)
Improvement[1]	78 (69%)	20 (36%)
No improvement	35 (31%)	36 (64%)
p-value[2]	< 0.0001	

[1] Improvement defined as ≥ 2-point decrease in Knodell necroinflammatory score from baseline at week 48 with no concurrent worsening fibrosis score.
[2] Compared to placebo (Chi-Square tests)
(Source: NDA 21-449, FDA analysis)

Population-based changes from baseline in Knodell necroinflammatory and fibrosis scores at week 48 in studies GS-98-437 and GS-98-438 are summarized in Tables 7.4.1.1E and 7.4.1.1F, respectively. In study GS-98-437, the median change in necroinflammatory scores at week 48 was -3 points in the ADV 30 mg group and -2 points in the ADV 10 mg group compared with 0 (unchanged) in the placebo group. The median fibrosis scores at week 48 remained unchanged in the adefovir-treated and placebo groups. In study GS-98-438, the median change in the necroinflammatory scores at week 48 was -3 in the ADV 10 mg group compared with no change in the placebo group. The median fibrosis scores at week 48 remained unchanged in adefovir-treated and placebo groups.

APPEARS THIS WAY
ON ORIGINAL

Table 7.4.1.1E. Population-Based Changes in Knodell Scores from Baseline at Week 48 in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Necroinflammation			
Baseline score			
Mean ± SD	7.84 ± 2.82	7.37 ± 2.75	7.83 ± 2.89
Median	8	7	8
Q1, Q3	7, 10	7, 9	7, 10
Week 48 score			
Mean ± SD	4.70 ± 2.63	4.80 ± 2.61	7.75 ± 2.61
Median	5	5	7
Q1, Q3	3, 7	3, 7	7, 10
Change in score at week 48			
Mean ± SD	-3.18 ± 3.28	-2.52 ± 3.24	-0.11 ± 3.07
Median	-3	-2	0
Q1, Q3	-5, 0	-5, 0	-2, 1
n	147	152	149
p-value	< 0.001	< 0.001	
Fibrosis			
Baseline score			
Mean ± SD	1.71 ± 1.06	1.64 ± 1.09	1.83 ± 1.12
Median	1	1	1
Q1, Q3	1, 3	1, 3	1, 3
Week 48 score			
Mean ± SD	1.42 ± 0.95	1.48 ± 0.97	1.85 ± 1.16
Median	1	1	1
Q1, Q3	1, 1	1, 1	1, 3
Change in score at week 48			
Mean ± SD	-0.31 ± 0.80	-0.18 ± 0.83	-0.01 ± 0.85
Median	0	0	0
Q1, Q3	0, 0	0, 0	0, 0
n	147	152	149

[1] Compared to placebo (Wilcoxon Rank Sum test)
(Source: NDA 21-449, Volume 112, Tables 21A-B, 22A-B, FDA analysis)

Table 7.4.1.1F. Population-Based Changes in Knodell Scores from Baseline at Week 48 in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Necroinflammatory score		
Baseline score		
Mean ± SD	7.73 ± 2.74	7.09 ± 2.71
Median	8	7
Q1, Q3	7, 10	5, 10
Week 48 score		
Mean ± SD	4.31 ± 2.41	7.25 ± 2.14
Median	3.5	7
Q1, Q3	2, 7	7, 9
Change in score at week 48		
Mean ± SD	-3.42 ± 2.86	0.27 ± 3.19
Median	-3	0
Q1, Q3	-6, -1	-2, 3
n	113	56
p-value[1]	< 0.001	
Fibrosis score		
Baseline score		
Mean ± SD	1.88 ± 1.17	1.81 ± 1.14
Median	1	1
Q1, Q3	1, 3	1, 3
Week 48 score		
Mean ± SD	1.60 ± 1.12	1.87 ± 1.11
Median	1	1
Q1, Q3	1, 3	1, 3
Change in score at week 48		
Mean ± SD	-0.29 ± 0.74	0.12 ± 0.93
Median	0	0
Q1, Q3	0, 0	0, 0
n	113	56

[1] Compared to placebo test (Wilcoxon Rank Sum test)
(Source: NDA 21-449, Volume 146, Tables 14A-B, 20A, 21A, FDA analysis)

Please refer to Dr. Rafia Bhore's statistical review for additional information on histologic endpoints.

7.4.1.2. Additional Analyses

The population-based mean change in the Knodell fibrosis score for all patients at week 48 presented above did not demonstrate a drug effect on liver fibrosis. As a result, additional analyses were performed by FDA to evaluate

the change in fibrosis from baseline at week 48 in studies GS-98-437 and GS-98-438 using both the Knodell and Ishak scoring systems. The Ishak scoring system is more sensitive in detecting changes in fibrosis. A change resulting in an increase in the fibrosis score of 1 or more (worse) or decrease in the score by 1 or more (improved) in either scoring system is taken as clinically relevant since it represents an appreciable increment of fibrosis. Results of these analyses are shown in Tables 7.4.1.2A and 7.4.1.2B.

Table 7.4.1.2A. Changes in Fibrosis Based on Knodell and Ishak Scores at Week 48 in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number of adequate biopsy pairs	147	152	149
Knodell fibrosis score			
Improved	29 (20%)	27 (18%)	15 (10%)
Unchanged	113 (77%)	114 (75%)	118 (79%)
Worse	5 (3%)	11 (7%)	16 (11%)
Ishak fibrosis score[1]			
Improved	61 (41%)	52 (34%)	28 (19%)
Unchanged	71 (48%)	83 (55%)	89 (60%)
Worse	15 (10%)	17 (11%)	32 (21%)

[1] Ishak fibrosis score is as follows: 0: no fibrosis; 1: fibrosis expansion of some portal areas; 2: fibrosis expansion of most portal areas; 3: fibrosis expansion of most portal areas with occasional portal-to-portal bridging; 4: fibrosis expansion of portal areas with marked bridging; 5: marked bridging with occasional nodules (incomplete cirrhosis); 6: cirrhosis, probable or definite.
(Source: NDA 21-449, FDA analysis)

Table 7.4.1.2.B. Changes in Fibrosis Based on Knodell and Ishak Scores at Week 48 in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Number of evaluable biopsy pairs	113	56
Knodell fibrosis score		
Improved	19 (17%)	5 (9%)
Unchanged	92 (81%)	43 (77%)
Worse	2 (2%)	8 (14%)
Ishak fibrosis score		
Improved	38 (34%)	8 (14%)
Unchanged	70 (62%)	28 (50%)
Worse	5 (4%)	20 (36%)

(Source: NDA 21-449, FDA analysis)

As shown above, in chronic hepatitis B patients who were HBeAg-positive (study GS-98-437), 60% of patients in the placebo group did not have appreciable changes in fibrosis after 48 weeks. Of the remaining patients, a slightly higher proportion (21%) experienced progression in fibrosis compared with 19% showing varying degrees of improvement (regression) in fibrosis. Of those who received adefovir treatment, there was a clear shift in favor of regression. Numerically, more patients had regression of fibrosis in the ADV 30 mg group (41%) than in the ADV 10 mg group (34%). The proportion of patients with worsening fibrosis was 10% and 11% for the ADV 30 mg group and ADV 10 mg group, respectively, or approximately half of that seen in the placebo group. These changes (between each treatment group versus placebo group) are statistically significant ($p < 0.001$).

In chronic hepatitis B patients who were HBeAg-negative (study GS-98-438), it is noted that within 48 weeks, an appreciably greater number of patients in the placebo group experienced progression in fibrosis (36%) than regression of fibrosis (14%). Since the number of available biopsy pairs was relatively fewer in this group (56 pairs versus > 100 pairs in other treatment groups), this observation should be interpreted with some caution. Nevertheless, it appears to be consistent with the clinical observation that HBeAg-negative chronic hepatitis B is characterized by continued necroinflammation in the liver and a more fluctuating disease course. In contrast, 34% of patients treated with adefovir had regression of fibrosis compared with 4% having progression in fibrosis. These changes are statistically significant ($p < 0.001$).

In study GS-98-437, 36 patients in the ADV 10 mg group, 69 in the ADV 30 mg group, and none in the placebo group had serum HBV DNA 400 copies/mL at week 48. In study GS-98-438, 64 patients in the ADV 10 mg group had serum HBV DNA 400 copies/mL at week 48. Numerically, a slightly higher number of these patients had improvement in the Ishak fibrosis scores compared with the overall figures of both studies (Table 7.4.1.2C).

Table 7.4.1.2C. Changes in Fibrosis Based on Ishak Scores in Patients with Serum HBV DNA 400 copies/mL at Week 48 in Studies GS-98-437 and GS-98-438

	GS-98-437		GS-98-438
	ADV 30 mg	ADV 10 mg	ADV 10 mg
Number of patients with HBV DNA 400 copies/mL:	69	36	64
Improved	33 (48%)	14 (39%)	27 (42%)
Unchanged	32 (46%)	21 (59%)	33 (52%)
Worse	4 (6%)	1 (3%)	4 (6%)

Reviewer's Comment

These observations appear to show that consecutive liver biopsies within a year of each other are a sensitive way to detect not only changes in necroinflammatory activity but also changes in fibrosis. The use of serum HBV DNA or ALT as endpoints in evaluating drug therapy for chronic hepatitis B would not demonstrate the drug's effect on the progression of fibrosis.

Ranked Assessment Analysis of Liver Biopsy:

The applicant also conducted blinded ranked assessment of histologic response to determine whether the baseline or week 48 biopsy of each patient was histologically "better," "unchanged," or "worse" for both studies. The analysis was based on the pathologist's "gestalt" opinion while comparing the baseline and week 48 biopsies, and not on a scoring system *per se*. Results of these assessments are summarized in Tables 7.4.1.2C and 7.4.1.2D for studies GS-98-437 and GS-98-438, respectively.

Table 7.4.1.2C. Ranked Assessment of Knodell Necroinflammatory and Fibrosis Scores in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number of adequate biopsy pairs	145 (87%)	150 (88%)	145 (84%)
Necroinflammatory			
"Better"	112 (77%)	107 (71%)	59 (41%)
"Unchanged"	18 (12%)	23 (15%)	37 (26%)
"Worse"	15 (10%)	20 (13%)	49 (34%)
Fibrosis			
"Better"	78 (54%)	62 (41%)	35 (24%)
"Unchanged"	53 (37%)	67 (45%)	72 (50%)
"Worse"	14 (10%)	21 (14%)	38 (26%)

(Source: NDA 21-449, Volume 112, Figure 2B)

Table 7.4.1.2D. Ranked Assessment of Knodell Necroinflammatory and Fibrosis Scores in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Number of adequate biopsy pairs	112 (91%)	55 (90%)
Necroinflammatory score		
"Better"	90 (80%)	23 (42%)
"Unchanged'	19 (17%)	4 (7%)
"Worse"	3 (3%)	28 (51%)
Fibrosis score		
"Better"	54 (48%)	14 (25%)
"Unchanged"	53 (47%)	20 (36%)
"Worse"	5 (4%)	21 (38%)

(Source: NDA 21-449, Volume 146, Figure 2A)

Reviewer's Comment

While the ranked assessment is an alternative way to interpret histologic changes in serial biopsies, it is relatively more subjective and operator-dependent than the structured scoring systems. Consequently, there were a number of discrepancies between the results obtained by the Knodell or Ishak scoring system and those by the ranked assessment. Table 7.4.1.2E illustrates, as an example, the inconsistency of ranked assessment versus Knodell and Ishak scoring systems in evaluating the change in fibrosis in study GS-98-438. In these cases, while both the baseline and week 48 liver biopsies had identical Knodell and Ishak scores (i.e., no changes in fibrosis), the ranked assessment rated one as being worse or better than the other.

Table7.4.1.2E. Change from Baseline in Fibrosis as Evaluated by the Knodell Scoring System, Ishak Scoring System, and Ranked Assessment in Study GS-98-438

Patient ID #	Baseline/Week 48 Fibrosis Score		Ranked Assessment Interpretation
	Knodell	Ishak	
338-2504	1/1	1/1	Baseline worse than week 48
338-2510	4/4	5/5	Baseline worse than week 48
341-3522	1/1	2/2	Week 48 worse than baseline
456-4502	1/1	1/1	Baseline worse than week 48
469-5544	1/1	2/2	Baseline better than week 48
474-5503	1/1	1/1	Baseline worse than week 48
477-5529	1/1	2/2	Baseline worse than week 48
480-5521	3/3	3/3	Baseline worse than week 48
499-2505	1/1	2/2	Baseline worse than week 48
511-4507	1/1	1/1	Baseline worse than week 48
624-1504	1/1	2/2	Baseline worse than week 48
624-1506	3/3	3/3	Baseline worse than week 48
624-1508	1/1	1/1	Baseline worse than week 48
624-1510	3/3	3/3	Baseline worse than week 48
624-1512	3/3	3/3	Baseline worse than week 48
624-1516	1/1	1/1	Baseline worse than week 48
624-1519	1/1	1/1	Week 48 better than baseline
624-1530	1/1	1/1	Baseline worse than week 48
624-1534	1/1	1/1	Baseline worse than week 48
625-1525	1/1	1/1	Baseline worse than week 48
625-1533	1/1	2/2	Baseline worse than week 48
626-1559	1/1	2/2	Baseline worse than week 48
627-1557	1/1	2/2	Baseline worse than week 48

(NDA 21-449, FDA analysis)

7.4.2. Virologic Response

Virologic responses, i.e., the time-weighted average change in serum HBV DNA (log_{10} copies/mL) from baseline up to week 48 ($DAVG_{48}$) and the proportion of patients with serum HBV DNA levels < 400 copies/mL, were the secondary efficacy endpoints of studies GS-98-437 and GS-98-438. In study GS-98-435, the time-weighted average change in serum HBV DNA from baseline up to week 24 ($DAVG_{24}$) was the primary efficacy endpoint. Virologic data of this study are still incomplete at the time of this review. Please see Dr. Bhore's review for additional information.

7.4.2.1.First 48 Weeks of Studies GS-98-437 and GS-98-438

Tables 7.4.2.1A and 7.4.2.1B summarize changes in serum HBV DNA from baseline to week 48 in studies GS-98-437 and GS-98-438, respectively.

Table 7.4.2.1A. Changes in Serum HBV DNA (log_{10} copies/mL) at Week 48 in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Baseline			
Mean ± SD	8.22 ± 0.84	8.25 ± 0.90	8.12 ± 0.89
Median	8.34	8.40	8.33
Q1, Q3	7.70, 8.81	7.69, 8.87	7.50, 8.76
n	173	171	167
Change (log_{10}) at week 48			
Mean ± SD	-4.38 ± 1.63	-3.52 ± 1.64	-0.99 ± 1.32
Median	-4.71	-3.38	-0.59
Q1, Q3	-5.47, 3.79	-4.82, -2.23	-1.71, -0.13
n	153	155	151
p-value[1]	< 0.001	< 0.001	
$DAVG_{48}$			
Mean ± SD	-4.05 ± 1.14	-2.98 ± 1.22	-0.68 ± 0.88
Median	-4.10	-2.84	-0.43
Q1, Q3	-4.82, -3.54	-3.86, -2.04	-0.97, -0.15
n	171	170	167
HBV DNA at week 48[2]			
≤ 400 copies/mL	69 (40%)	36 (21%)	0 (0%)
> 400 copies/mL	84 (48%)	119 (70%)	151 (90%)
n	153	155	151

[1] Compared with placebo (Student's t test)
[2] Missing serum HBV DNA data treated as > 400 copies/mL
(Source: NDA 21-449, Volume 112, Tables 27, 29, and 31; FDA analysis)

In study GS-98-437, the median change from baseline at week 48 in serum HBV DNA was -4.71 log_{10} copies/mL and -3.38 log_{10} copies/mL in the ADV 30 mg group and ADV 10 mg group, respectively, compared with -0.59 log_{10} copies/mL in the placebo group. Expectedly, the median time-weighted average change in serum HBV DNA (log_{10} copies/mL) from baseline up to week 48 ($DAVG_{48}$) was higher in the adefovir treatment groups than in the placebo group. The proportion of patients with serum HBV DNA below the lower limit of quantification (less than 400 copies/mL) was also higher in the adefovir groups than in the placebo group.

Table 7.4.2.1B. Changes in Serum HBV DNA (log_{10} copies/mL) at Week 48 in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Baseline HBV DNA		
Mean ± SD	6.92 ± 0.86	6.93 ± 0.95
Median	7.10	7.05
Q1, Q3	3.67, 9.46	4.42, 8.45
n	123	61
Change (log_{10}) at week 48		
Mean ± SD	-3.54 ± 1.16	-1.23 ± 1.27
Median	-3.83	-1.30
Q1, Q3	-4.38, -2.65	-2.03, -0.35
n	119	56
p-value	< 0.001	
$DAVG_{48}$	-3.38 ± 0.89	-1.13 ± 0.84
Mean ± SD	-3.53	-0.87
Median	-4.09, -2.79	-1.57, -0.52
Q1, Q3	123	61
n		
HBV DNA at week 48[2]		
≤ 400 copies/mL	64 (52%)	0 (0%)
> 400 copies/mL	55 (45%)	56 (92%)
n	119	56

[1] Compared with placebo (Student's t test)
[2] Missing serum HBV DNA data treated as > 400 copies/mL
(Source: NDA 21-449, Volume 146, Tables 27 and 29; FDA analysis)

In study GS-98-438, the median change from baseline at week 48 in serum HBV DNA was -3.83 log_{10} copies/mL in the ADV 10 mg group compared with -1.30 log_{10} copies/mL in the placebo group. The median $DAVG_{48}$ in serum HBV DNA and the proportion of patients with serum HBV DNA below the lower limit of quantification was also higher in the adefovir group than in the placebo group.

7.4.2.2.Second 48 Weeks of Studies GS-98-437 and GS-98-438

Study GS-98-437 was originally designed to compare the effect of 48 weeks versus 96 weeks of treatment with adefovir by having the following treatment crossover sequences: placebo in the first 48 weeks to be followed by adefovir 10 mg daily in the second 48 weeks; adefovir 10 mg daily in the first 48 weeks to be followed by placebo or adefovir 10 mg daily in the second 48 weeks; and adefovir 30 mg daily in the first 48 weeks to be followed by placebo in the second 48 weeks. However, due to study medication errors, a total of 393 patients who were randomized to the second 48 weeks of the

study received at least one incorrect dose, and one patient discontinued prior to receiving incorrect medication.

Because of this error, the study was unblinded and all patients were offered the option to receive open-label treatment with adefovir 10 mg daily for a minimum of 16 weeks until commencement of a roll-over study. Patients who had HBeAg or HBsAg seroconversion, HBeAg or HBsAg loss with normalized ALT and suppressed serum HBV DNA levels were offered enrollment into study GS-00-481 for long-term off-drug observation.

The applicant conducted an interim analysis of serum HBV DNA data from the second 48 weeks (median of 16.1 weeks, range from 0.1 to 48.1 weeks). The analysis was based on actual study medication received and included data from the first dose of the second 48 week study medication until the earliest occurrence of permanent discontinuation, the first incorrect study medication, or study day 686 (the upper bound of week 96 study visit window). Results of this analysis up to week 36 are summarized in Table 7.4.2.2A (data after this time point were grossly insufficient for inclusion).

In study GS-98-437, an additional 24 weeks of treatment with adefovir 10 mg daily (for a total of 72 weeks) resulted in an additional median decrease from baseline (of the second 48 week) in serum HBV DNA of -0.21 $\log_{10}$ copies/mL. The median change in serum HBV DNA from baseline in the placebo-to-ADV 10 mg group during the second 48 weeks appeared to be comparable to that seen in the ADV 10 mg group of the first 48 weeks. Patients who were switched from ADV 30 mg group or ADV 10 mg group to placebo group experienced a return of serum HBV DNA to baseline levels within 4 to 8 weeks. These are summarized in Table 7.4.2.2A.

In study GS-98-438, additional 24 weeks of treatment with adefovir 10 mg daily did not produce further decrease in serum HBV DNA. The change from baseline in serum HBV DNA in the second 48 weeks of this study is summarized in Table 7.4.2.2B.

Table 7.4.2.2A. Serum HBV DNA Change from Baseline ~~in the Second~~ 48 Weeks in Study GS-98-437

	Treatment Assignment			
	ADV 30 mg to placebo	ADV 10 mg to placebo	ADV 10 mg to ADV 10 mg	Placebo to ADV 10 mg
Number of patients	142	70	85	138
Baseline				
Median	2.96	4.10	5.12	7.57
Q1, Q3	2.60, 4.48	2.76, 5.61	2.83, 6.28	6.45, 8.35
n	142	70	85	138
Week 12				
Median	3.17	1.76	-0.13	-2.32
Q1, Q3	1.47, 4.53	0.85, 2.52	-0.45, 0.00	-3.12, -1.62
n	98	46	54	95
Week 24				
Median	3.16	1.50	-0.21	-2.67
Q1, Q3	1.17, 4.20	0.76, 3.21	-0.69, -0.04	-3.71, -2.08
n	50	19	29	46
Week 36				
Median	3.84	1.57	-0.53	-2.93
Q1, Q3	1.61, 4.94	0.00, 2.77	-0.59, 0.26	-3.97, -1.38
n	12	10	9	11

(Source: NDA 21-449, Volume 114, supporting tables for Figures 5A1 and 5B1)

Table 7.4.2.2B. Serum HBV DNA Change from Baseline in the Second 48 Weeks in Study GS-98-438

	Treatment Group		
	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	Placebo to ADV 10 mg
Number of ITT patients	79	40	60
Baseline			
Median	2.60	2.66	5.68
Q1, Q3	2.60 to 3.34	2.60 to 3.46	4.61 to 6.70
n	79	40	60
Week 12			
Median	0.00	1.76	-2.18
Q1, Q3	-0.07 to 0.00	0.86 to 2.99	-2.84 to -1.72
n	78	39	59
Week 24			
Median	0.00	1.53	-2.65
Q1, Q3	-0.17 to 0.00	0.75 to 3.82	-3.24 to -1.95
n	36	18	27

(Source: NDA 21-449, Volume 147, Supporting table for Figures 5A.1 and 5A.2)

7.4.2.3. Study GS-98-435

Patients in this study had lamivudine-resistant HBV. A summary of change from baseline in serum HBV DNA for cohorts 1A, 2A, and 3A (post-liver transplantation) is presented in Table 7.4.2.3A. Since patients in cohort 2A were previously receiving adefovir in study GS-98-451i upon enrollment into this study, their serum HBV DNA levels were already suppressed. Additionally, some patients in this study received adefovir 5 mg daily or less due to their renal dysfunction. The change from baseline in serum HBV DNA by study visit for patients in cohorts 1B, 2B, and 3B (waitlisted for liver transplantation) is summarized in Table 7.4.2.3B. Similarly, patients in cohort 2B were also previously treated with adefovir.

Table 7.4.2.3A. Serum HBV DNA Change from Baseline in Post-Liver Transplantation Patients during the First 48 Weeks in Study GS-98-435

	Treatment Group			
	1A	2A	3A	Total
Number of patients	117	12	67	196
Baseline (log_{10} copies/mL)				
Median	8.3	3.8	8.1	8.1
Q1, Q3	7.7, 8.9	3.2, 5.2	7.5, 8.8	7.4, 8.8
n	68	9	33	110
Change in log_{10} HBV DNA				
Week 4				
Median	-2.1	-0.1	-2.1	-2.0
Q1, Q3	-3.1, -2.1	-0.5, 0	-2.8, -1.5	-2.5, -1.3
n	67	8	32	107
Week 8				
Median	-2.7	-0.5	-2.6	-2.6
Q1, Q3	-4.2, 0.1	-0.6, 0.1	-3.4, -1.8	-3.1, -1.9
n	65	7	29	101
Week 12				
Median	-2.9	-0.4	-3.1	-2.9
Q1, Q3	-3.6, -2.5	-0.6, 0	-3.8, -2.5	-3.6, -2.2
n	64	7	28	99
Week 24				
Median	-3.5	-0.6	-3.7	-3.5
Q1, Q3	-5.0, -3.0	-0.6, -0.3	-4.8, -3.2	-4.9, -3.0
n	55	3	26	84
Week 36				
Median	-3.9	-0.4	-3.5	-3.7
Q1, Q3	-6.6, -1.7	-0.9, 0	-5.1. -3.1	-5.0, -3.0
n	43	4	23	70
Week 48				
Median	-4.4	-0.6	-3.9	-4.3
Q1, Q3	-5.5, -3.6	-0.8, -0.5	-5.6, -3.0	-5.4, -3.0
n	28	3	15	46

(Source: NDA 21-449, NDA Safety Update, Volume 2, Table 21)

APPEARS THIS WAY
ON ORIGINAL

Table 7.4.2.3B. Serum HBV DNA Change from Baseline in Patients Waitlisted for Liver Transplantation during the First 48 Weeks in Study GS-98-435

	Treatment Group			
	1B	2B	3B	Total
Number of patients	46	2	80	128
Baseline (log_{10} copies/mL)				
Median	7.5	5.2	7.4	7.4
Q1, Q3	6.6, 8.1	3.1, 7.3	6.5, 8.1	6.6, 8.1
n	42	2	66	110
Change in log_{10} HBV DNA				
Week 4				
Median	-2.3	-0.7	-2.2	-2.2
Q1, Q3	-2.6, -1.6	-1.4, -0.1	-3.0, -1.5	-2.7, -1.5
n	41	2	55	98
Week 8				
Median	-2.8	-0.7	-2.8	-2.8
Q1, Q3	-3.4, -2.0	-1.4, -0.1	-3.5, -2.1	-3.4, -2.0
n	40	2	49	91
Week 12				
Median	-3.2	-1.4	-2.9	-3.0
Q1, Q3	-4.2, -2.5	-2.7, -0.1	-3.7, -2.1	-3.8, -2.2
n	38	2	44	84
Week 24				
Median	-4.1	-2.8	-3.7	-3.7
Q1, Q3	-4.6, -2.9	-2.8, -2.8	-4.4, -2.6	-4.5, -2.6
n	21	1	30	52
Week 36				
Median	-4.6	-	-3.9	-4.2
Q1, Q3	-5.0, -3.4	-	-4.4, -3.0	-4.9, -3.0
n	30	0	43	75
Week 48				
Median	-4.8	-	-3.9	-4.1
Q1, Q3	-4.9, -4.6	-	-4.3, -3.4	-4.6, -3.5
n	3	0	10	13

(Source: NDA 21-449, NDA Safety Update, Volume 2, Table 22)

Reviewer's Comment

While the available HBV DNA data of this study were limited to less than 68% of patients, it appears that adefovir treatment resulted in a virologic suppression of lamivudine-resistant HBV comparable to that of wild-type HBV.

7.4.3. Biochemical Response [redacted]

Changes from baseline in ALT of study GS-98-437 are summarized in Table 7.4.3A and those in study GS-98-438 are summarized in Table 7.4.3B. The median baseline ALT of patients in study GS-98-437 was approximately 2.3 x ULN which indicated active liver cell injury. At week 48, the median reduction from baseline in ALT was 54 U/L in the ADV 30 mg group and 51 U/L in the ADV 10 mg group compared with 17 U/L in the placebo group. Similarly, in study GS-98-438, the median reduction from baseline at week 48 in ALT was 55 U/L in the ADV 10 mg group compared with 38 U/L in the placebo group.

The proportion of patients with normalization of serum ALT at week 48 was one of the key secondary endpoints in this study. In study GS-98-437, approximately 55% of patients in the ADV 30 mg group and 48% in the ADV 10 mg group experienced normalization of ALT at week 48, compared with 16% in the placebo group. The proportion of patients with normalization of ALT at week 48 in study GS-98-438 was 72% in the ADV 10 mg group, compared with 29% in the placebo group.

Please also see Dr. Bhore's review for additional information.

APPEARS THIS WAY
ON ORIGINAL

Table 7.4.3A. ALT Change from Baseline at Week 48 in Study GS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Baseline value (U/L)			
Mean ± SD	123.8 ± 96.3	138.8 ± 153.6	139.0 ± 131.2
Median	92.0	95.0	94.0
Q1, Q3	63, 147	65, 165	69, 159
n	173	171	167
Change at week 24			
Mean ± SD	-66.2 ± 111.2	-79.0 ± 169.7	-20.5 ± 136.9
Median	-37.0	-38.0	-7.0
Q1, Q3	-99, -7	-97, -11	-42, 22
n	159	158	157
Change at week 44			
Mean ± SD	-73.3 ± 126.8	-88.8 ± 163.1	-24.8 ± 158.1
Median	-53.0	-49.0	-12.0
Q1, Q3	-106, -16	-120, -20	-56, 14
n	151	159	150
Change at week 48			
Mean ± SD	-74.4 ± 128.4	-89.5 ± 166.6	-22.5 ± 13.3
Median	-54.0	-48.0	-17.0
Q1, Q3	-106, -16	-113, -18	-57, 13
n	144	155	151
Proportion of patients at weeks 48 with:			
Normalized ALT value	93 (54%)	81 (47%)	26 (16%)
Not normalized value[1]	80 (46%)	90 (52%)	141 (84%)

[1] Missing ALT data treated as not normalized.
(Source: NDA 21-499, Volume 112, Table ; FDA analysis)

APPEARS THIS WAY
ON ORIGINAL

Table 7.4.3A. ALT Change from Baseline at Week 48 in Study ~~GS-98-438~~

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Baseline value (U/L)		
Mean ± SD	143.5 ± 125.3	149.8 ± 195.1
Median	93.0	100.0
Q1, Q3	69, 165	72, 161
n	123	61
Change at week 24		
Mean ± SD	-103.4 ± 129.0	-67.5 ± 224.9
Median	-58.0	-33.0
Q1, Q3	-127, -32	-85, 3
n	117	57
Change at week 48		
Mean ± SD	-99.7 ± 122.2	-76.8 ± 211.5
Median	-55.0	-38.0
Q1, Q3	-134, -30	-91, -9
n	120	56
Proportion of patients at week 48 with:		
Normalized ALT value	84 (68%)	17 (28%)
Not normalized value[1]	39 (32%)	44 (72%)

[1] Missing ALT data treated as not normalized.
(Source: NDA 21-499, Volume 146, Table ; FDA analysis)

7.4.4. HBeAg and HBsAg Seroconversion

In the first 48 weeks of study GS-98-437, HBeAg seroconversion, defined as a loss of HBeAg with concurrent gain in anti-HBe antibody (HBeAb), occurred in 26 patients (17%, 95% CI of 10.9-22.7) in the ADV 30 mg group, and 23 patient (14%, 95% CI of 8.5-18.8) in the ADV 10 mg group, compared with 14 patients (9%, 95% CI of 4.6-14.0) in the placebo group at week 48. The median time to seroconversion was 11, 20, and 32 weeks for the ADV 30 mg group, ADV 10 mg group, and placebo group, respectively (see Table 7.4.4).

Table 7.4.4. Kaplan-Meier Analysis of Time to HBeAg Seroconversion

	Treatment Group					
	ADV 30 mg (n = 163)		ADV 10 mg (n = 170)		Placebo (n = 161)	
	Cum. events	KM%	Cum. events	KM%	Cum. events	KM%
Baseline	0	0%	0	0%	0	0%
> Baseline - week 4	1	1%	1	1%	0	0%
> Week 4 - week 8	9	6%	4	2%	0	0%
> Week 8 - week 12	13	8%	6	4%	1	1%
> Week 12 - week 16	16	10%	7	4%	4	3%
> Week 16 - week 20	17	10%	9	5%	4	3%
> Week 20 - week 24	17	10%	13	8%	4	3%
> Week 24 - week 28	18	11%	15	9%	5	3%
> Week 28 - week 32	18	11%	16	9%	7	4%
> Week 32 - week 36	20	12%	18	11%	11	7%
> Week 36 - week 40	22	14%	20	12%	12	8%
> Week 40 - week 44	22	14%	22	13%	13	8%
> Week 44 - week 48	26	17%	23	14%	14	9%

(Source: NDA 21-449, Volume 112, Supporting Table for Figure 4)

Following seroconversion, approximately 85.5% of patients on adefovir treatment (96% in the ADV 30 mg group and 75% in the ADV 10 mg group) had HBV DNA levels less than 1,000 copies/mL at week 48. However, none of the patients with HBeAg seroconversion in the placebo group had HBV DNA levels lower than this value. The majority of patients who had HBeAg seroconversion (83.5% in the adefovir groups and 56% in the placebo group) had normalization of ALT at week 48.

Of the 385 patients who did not seroconvert during the first 48 weeks, an additional 12 patients (14% by Kaplan-Meier estimate) in the placebo to ADV 10 mg group, 4 patients (7% by K-M estimate) in the ADV 10 mg to ADV 10 mg group, 7 patients (20% by K-M estimate) in the ADV 10 mg to placebo group, and 12 patients (18% by K-M estimate) in the ADV 30 mg to placebo group experienced HBeAg seroconversion. All seroconversions occurred by weeks 24, 16, 20, and 26, respectively, in the second 48 weeks of the study.

No patients in study GS-98-437 had HBsAg seroconversions (defined as a loss of HBsAg with concurrent gain of HBsAb) at the time of this analysis. During the second 48 weeks of study GS-98-438, one patient experienced HBsAg seroconversion at week 72.

Reviewer's Comment

Adefovir treatment is associated with HBeAg seroconversion rates of 17% in the ADV 30 mg group and 14% in the ADV 10 mg group at week 48. These rates are comparable to those receiving lamivudine therapy (17% at one year). At present, it remains unclear whether adefovir-associated HBeAg seroconversion is durable after treatment is discontinued. Treatment also appeared to show a dose-related acceleration of time to seroconversion.

7.5. Conclusions

With respect to the evidence of effectiveness, adefovir treatment compared with placebo resulted in:

- statistically significant improvement in liver histology (defined as 2-point improvement in the Knodell necroinflammatory score without concomitant worsening of fibrosis score) at week 48 (studies GS-98-437 and GS-98-438),
- statistically significant improvement in liver fibrosis (defined as a decrease in the Ishak fibrosis score by 1 or more) at week 48 (studies GS-98-437 and GS-98-438),
- statistically significant suppression of HBV replication over time as shown by serial serum HBV DNA levels using an experimental PCR assay (studies GS-98-437 and GS-98-438),
- higher proportion of patients with serum HBV DNA suppression to 400 copies/mL at week 48 (studies GS-98-437 and GS-98-438),
- higher proportion of patients with progressive decrease in serum ALT levels over time (studies GS-98-437 and GS-98-438),
- higher proportion of patients with normalization of ALT levels at week 48 (studies GS-98-437 and GS-98-438),
- higher proportion of patients with HBeAg seroconversion (defined as loss of HBeAg and gain of anti-HBe antibody) over time (study GS-98-437), and
- comparable suppression of lamivudine-resistant HBV and wild-type HBV replication over time (study GS-98-435).

The treatment effects were quantitatively higher in the ADV 30 mg group compared to those in the ADV 10 mg group (study GS-98-437). However, except for serum HBV DNA parameters, the treatment effect differences between these two groups were not statistically significant.

8. Review of Safety Data

Safety data from three studies, GS-98-437, GS-98-438, and GS-98-435, will be reviewed in detail in this section.

8.1. Deaths

8.1.1. Study GS-98-437

Three deaths have been reported in study GS-98-437 after the clinical data cutoff date:

- The first case involved a 55-year-old black male (ID # 0330-1073) who was enrolled on September 2, 1999, and randomized to receive adefovir 30 mg daily in the first 48 weeks of the study. On July 24, 2000, the adefovir dose was reduced to 10 mg daily due to an increase in serum creatinine from 0.8 mg/dL at baseline to 1.2 mg/dL. On September 18, 2000, the patient was re-randomized to receive placebo for the second 48 weeks. Due to misallocation of study drug, he received placebo alternating with adefovir 10 mg daily. Early in February 2001, he presented with lymphadenopathy, anorexia, and malaise. On February 20, 2001, he was hospitalized with findings of hypercalcemia (16.1 mg/dL), hypophosphatemia (2.1 mg/dL), and elevated serum creatinine to 2.4 mg/dL. Study drug was discontinued. A work-up revealed stage III T-cell non-Hodgkin's lymphoma and HTLV-1 infection. Subsequently, he developed sepsis, multiple organ failure, and expired. The death was considered by the investigator as unrelated to study drug.

- The second case involved a 69-year-old male (ID # 0473-6046) with a history of cardiomyopathy who received placebo in the first 48 weeks and adefovir 10 mg daily in the second 48 weeks. Approximately 11 weeks of adefovir treatment, the patients developed acute cardiac failure and died. The investigator considered the death was possibly/probably related to treatment.

- The third case involved a 28-year-old Asian man who completed 96 weeks of adefovir treatment. Subsequently, he commenced the open-label phase and started adefovir 10 mg daily in October 2001. On July 19, 2002 patient reportedly "died in his sleep." No autopsy was performed. The coroner indicated the cause of death as "pancreatitis based on patient's history."

8.1.2. Study GS-98-438 [redacted]

There was one death reported in study GS-98-438. The patient was a 47-year-old black male (ID # 1223-5509) who was diagnosed with hepatocellular carcinoma at the beginning of the second 48 weeks of treatment. Nevertheless, he completed 96 weeks of adefovir 10 mg daily and began lamivudine treatment. He subsequently underwent a liver transplantation. Twenty-four hours after surgery, the patient's ALT peaked at 4,000 U/L and acute renal failure developed necessitating dialysis. He was found to have a collapsed hepatic artery with necrosis of the right hepatic lobe requiring a second liver transplant and splenectomy. His condition continued to deteriorate and he subsequently died of disseminated mycosis. The investigator considered the patient's death as unrelated to study drug.

8.1.3. Study GS-98-435

As of February 28, 2002, 390 patients were enrolled in study GS-98-435. Of these, a total of 42 (11%) patients, 18 in subcohort A (post-liver transplantation), and 24 in subcohort B (waitlisted for liver transplantation), had died. According to the applicant's report, all but one death (patient ID # 506-2339) were considered by the investigator as unrelated to study drug. However, several of these deaths are of concern, particularly in light of the recently available pharmacokinetic results of adefovir in renally impaired patients, since the terminal events could have been associated with adefovir-induced nephrotoxicity.

In chronic hepatitis B patients with intact renal function, the mean (geometric) area under the curve (AUC_{0-}) and the C_{max} of adefovir following multiple oral doses of adefovir 10 mg daily are approximately 200 ± 41 ng.hr/mL and 18 ± 3 ng/mL, respectively. However, results of a recently completed pharmacokinetic study GS-00-473 (summarized below) showed that renally impaired patients had significantly greater adefovir blood exposure after a single dose of adefovir 10 mg.

	Renal Function Status by Creatinine Clearance (mL/min)			
	Unimpaired > 80 (109 ± 25)	Mild 50-79 (66 ± 16)	Moderate 30-49 (40 ± 9)	Severe < 30 (18 ± 6)
Median AUC_{0-} (ng.hr/mL)	200 ± 41	266 ± 56	455 ± 176	1244 ± 629
Median C_{max} (ng/mL)	18 ± 3	22 ± 4	28 ± 9	52 ± 10

Consequently, the applicant has recently proposed the following dose interval adjustment of adefovir in patients with renal dysfunction based on baseline creatinine clearance (please see Dr. Kumi's biopharmaceutic review for additional information):

	Creatinine Clearance (mL/min)			
	50	20 to 49	10 to 19	Dialysis
Recommended dose/dosing interval	10 mg q 24 hrs	10 mg q 48 hrs	10 mg q 72 hrs	10 mg q 7 days following dialysis

Since a number of patients in study GS-98-435 had various degrees of renal dysfunction, they were probably exposed to higher blood levels of adefovir than intended while receiving adefovir 10 mg daily dose. As a result, the renal events in some patients who died in study GS-98-435 were of special review interest. These and other noteworthy cases are summarized below.

- Case # 1 (Patient ID # 451-2013; cohort 1A): This 65-year-old white male status post liver transplant on December 5, 1991, started adefovir 10 mg daily on November 1, 1999. Baseline laboratory results were: ALT 408 U/L; total bilirubin 1.7 mg/dL; albumin 2.8 g/L; creatinine 1.9 mg/dL; calculated creatinine clearance 40.3 mL/min; phosphorus 2.3 mg/dL; HBV DNA 7.03 $\log_{10}$ copies/mL; and Child-Pugh score 6. Concomitant medications included cyclosporine, sirolimus, co-trimoxazole, and furosemide.

  Relevant laboratory test results were as follows:

Date:	11/99	01/00	03/00	04/00	08/00	11/00	12/00
Creatinine:	1.9	2.5	3.0	2.9	3.1	4.7	6.1
Cr. Cl.	40.3	29.9	25.2	26.1	24.6	25.3	2.6

  On May 23, 2000, the adefovir dose was reduced to 5 mg daily as serum creatinine increased to 3.0 mg/dL. Following dose reduction, serum HBV DNA levels remained suppressed. In July 2000, serum HBV DNA was 2.60 $\log_{10}$ copies/mL. On November 27, 2000, the patient was hospitalized with confusion. Laboratory testing showed ALT 229 U/L, AST 418 U/L, PT 15.7 seconds, plasma ammonia 48 µg/dL (?) (reference range: 15-50 µg/dL). Upon treatment, his mental status improved. A liver biopsy showed moderate chronic hepatitis and superimposed acute rejection. On December 2, 2000, laboratory testing revealed creatinine of 6.4 mg/dL. Eleven days later, the patient began dialysis for renal failure. Adefovir dosing was reduced to 5 mg every other day. On December 28, 2000, he developed respiratory arrest and expired.

Reviewer's Comment

This patient had moderate renal impairment at baseline (creatinine clearance of 40.3 mL/min). Subsequent to adefovir therapy at the dose of 10 mg daily, his renal function progressively deteriorated. While other confounding factors were also present, in light of the pharmacokinetic results described earlier, it is likely that adefovir could have contributed to the initial increase in serum creatinine.

- Case # 2 (Patient ID # 1028-2050; cohort 1A): This 58-year-old white male status post liver transplant on August 9, 1998, started adefovir 10 mg daily on August 10, 2000. Baseline laboratory results were: ALT 164 U/L; total bilirubin 1.9 mg/dL; albumin 3.4 g/dL; BUN 47 mg/dL; creatinine 1.2 mg/dL; and calculated creatinine clearance 66.3 mL/min. Concomitant medications included lamivudine, tacrolimus, clonidine, prednisone, famotidine, and furosemide. On September 1, 2000, the patient was started on furosemide for pedal edema. Five days later, he was hospitalized for abdominal pain, nausea, vomiting, diarrhea, dehydration, and was found to have serum tacrolimus level of 41.6 µg/L (target therapeutic level: 5-15 µg/L). Tacrolimus was temporarily discontinued. Laboratory tests on September 5, 2000, revealed creatinine 3.1 mg/dL, BUN 73 mg/dL, ALT 233 U/L, total bilirubin 5.5 mg/dL, albumin 2.6 g/dL, and creatinine clearance of 28.0 mL/min. On September 13, 2000, the adefovir dose was reduced to 5 mg daily. The patient was found unresponsive the next day and subsequently expired on September 15, 2000. Autopsy revealed recurrent necrotizing hepatitis and probable ischemic colitis. The investigator assessed the event as possibly related to adefovir and death due to underlying liver disease.

  Reviewer's Comment

  The baseline creatinine clearance in this patient, 66.3 mL/min, suggested underlying renal impairment. His serum creatinine rapidly increased and the creatinine clearance was virtually halved within a month of adefovir treatment. While possible, it was not completely clear whether adefovir taken at the dose of 10 mg daily for less than a month could have been the main contributor to the renal event in this patient.

- Case # 3 (Patient ID # 481-2357; cohort 3B): This 62-year-old male started adefovir 10 mg daily on March 27, 2001. Baseline laboratory results were: ALT 219 U/L; total bilirubin 36.0 mg/dL; albumin 3.7 g/L; creatinine 1.6 mg/dL; PT 21.2 seconds; calculated creatinine clearance 68.6 mL/min; phosphorus 2.8 mg/dL; HBV DNA 7.07 $\log_{10}$ copies/mL; and Child-Pugh score 10. Concomitant medications included lamivudine, rifaximin, lactulose, dopamine, omeprazole, ursedeoxycholic acid, and doxazosin. On March 31, 2001, the patient had clinical signs of hepatic encephalopathy. Laboratory tests were noted for serum creatinine of 2.2 mg/dL, BUN of 79 mg/dL, ALT

of 198 U/L, and total bilirubin of 37.8 mg/dL. On April 1, 2001, the patient became anuric with a maximal creatinine of 4.6 mg/dL. Adefovir treatment was discontinued. A consulting nephrologist suggested that an acute toxic insult might have led to acute renal failure. The investigator assessed that adefovir was a possible/probable causal factor due to the temporal relationship. The patient subsequently suffered a cardiopulmonary arrest later that day and died the next day.

Reviewer's Comment

It is unclear in this case whether adefovir was indeed the acute toxic insult that led to acute renal failure in this patient with pre-existing renal function impairment. However, it could have played a contributory role in the event.

- Case # 4 (Patient ID # 545-2310; cohort 3B): A 43-year-old white male on the waiting list for liver transplant started adefovir 10 mg daily on October 17, 2000. Baseline laboratory results were: ALT 171 U/L; total bilirubin 5.1 mg/dL; albumin 1.8 g/L; creatinine 0.7 mg/dL; and calculated creatinine clearance 144.3 mL/min. Significant medical history included myalgia, leg cramps, and elevated creatine kinase (270 U/L on October 16, 2001). Laboratory testing on October 19, 2000, showed creatine kinase 484 U/L, and myoglobin 90 µg/mL. Adefovir treatment was interrupted. By October 22, 2000, creatine kinase values had returned to normal and adefovir was restarted the next day. After restating the study drug, the leg cramps increased in intensity. Adefovir treatment was once again interrupted. On November 20, 2000, adefovir was restarted. On December 1, 2000, the patient had an acute episode of esophageal hemorrhage requiring vasopressors, fresh frozen plasma, platelets, and coagulant factor infusion. He apparently developed metabolic acidosis, acute renal failure, and anuria. Dialysis was started. On December 2, 2000, he had liver transplantation surgery and was started on cyclosporine and basiliximab. The adefovir dose was changed to 10 mg three times weekly. His hospital course was stormy with sepsis, fever of unknown origin, pleural effusion, cholestasis, epistaxis, cytomegalovirus and herpes simplex virus infection. Laboratory testing on January 11, 2001 revealed a serum creatinine of 4.7 g/dL. His last dialysis was on January 25, 2001. He was discharged from the hospital on February 8, 2001 with a serum creatinine of 3.6 mg/dL. On April 9, 2002, the serum creatinine was 2.8 mg/dL.

Reviewer's Comment

The acute episode of esophageal hemorrhage in December 2000 and the subsequent hemodynamic complications most likely precipitated the acute renal failure in this patient. The potential contributory role of adefovir was not clear in this case.

- Case # 5 (Patient ID # 506-2339; cohort 3B): This 40-year-old male started adefovir 10 mg daily on January 20, 2001. Baseline laboratory results were: ALT 106 U/L; total bilirubin 26.7 mg/dL; albumin 2.0 g/L; creatinine 0.87 mg/dL; PT 23.6 seconds; and HBV DNA 390 pg/mL. Concomitant medications included lamivudine, propoxyphene, and levofloxacin. Prior to adefovir therapy, his creatinine levels were between 0.6 and 1.2 mg/dL.

  Relevant laboratory test results were as follows:

Date:	01/17	01/19	01/20	01/21	01/30	02/20	02/24	02/25
Creatinine:	0.87	0.98	1.01	1.03	1.21	1.86	4.04	5.09
Bilirubin:	11.3	26.7	45.9	45.9	21.3	45.9	52.6	50.9

  On February 21, 2001, the adefovir dose was reduced to 5 mg daily. The patient was thought to develop hepatorenal syndrome and expired on February 26, 2001. The investigator could not rule out study drug as a possible contributory factor to the patient's demise.

  Reviewer's Comment

  Hepatorenal syndrome was likely the terminal event in this case.

- Case # 6 (Patient ID # 536-2130; cohort 3B): A 42-year-old white male who was co-infected with HIV and lamivudine-resistant HBV previously received adefovir for HIV from November 23, 1999 (baseline serum creatinine 0.9 mg/dL) to October 3, 2001. Serum creatinine on October 30, 2001 was 1.2 mg/dL. On January 21, 2002, his screening serum creatinine was 1.4 mg/dL. The patient was reportedly hospitalized the next day with reactivation of hepatitis B disease, hepatorenal syndrome, HIV, abdominal pain, and mental status changes. On January 25, 2002, adefovir 5 mg daily dose was started with baseline serum creatinine 2.6 mg/dL, ALT 265 U/L, AST 705 U/L, total bilirubin 25.5 mg/dL, albumin 2.8 g/dL, and PT 38.7 seconds. On January 30, 2002, his serum creatinine increased to 5.5 mg/dL. On January 31, 2002, the serum creatinine reached 6.2 mg/dL, BUN 78 mEq/L, and total bilirubin 51.3 mg/dL. The patient expired the next day. The investigator assessed the event as unrelated to adefovir.

  Reviewer's Comment

  It appears that the onset of hepatorenal syndrome in this patient occurred prior to adefovir administration.

- Case # 7 (Patient ID # 560-2419; cohort 3B): This 41-year-old male status post liver transplant on October 16, 1997, started adefovir 10 mg daily on September 5, 2001. Baseline laboratory results were: ALT 116 U/L; total bilirubin 1.2 mg/dL; albumin 2.0 g/L; PT 15.4 seconds; creatinine 0.9 mg/dL;

calculated creatinine clearance 148.2 mL/min; phosphorus 3.6 mg/dL; Child-Pugh score 6; and HBV DNA 390 pg/mL. Concomitant medications included lamivudine, tacrolimus, and famciclovir. On November 9, 2001, he was hospitalized due to jaundice. The ALT level was 3 x ULN and AST 4.7 x ULN, and he was diagnosed with "hepatic flare" due to HBeAg seroconversion. Adefovir was discontinued on November 26, 2001. The patient subsequently died on November 27, 2001. Autopsy revealed cirrhosis, extensive gastrointestinal and subarachnoid hemorrhage. A physician opined that the hepatic decompensation was possibly related to study drug.

Reviewer's Comment

This case speaks to the need for close monitoring of patients for hepatic flare due to seroconversion during treatment.

8.2. Other Serious Adverse Events

8.2.1. Study GS-98-437

In the first 48 weeks of the study, eight patients (5%) in the ADV 30 mg group, eleven patients (6%) in the ADV 10 mg group, and nine patients (5%) in the placebo group experienced serious adverse events (see Table 8.2.1A). With the exception of three patients (ID # 0381-1020, 0477-6044, and 0505-6080) who had elevated transaminases (ALT and/or AST), all of these serious adverse events resulted in hospitalization. Approximately 29% of these events were considered by the investigators as related to adefovir treatment.

Table 8.2.1A. Serious Adverse Events in the First 48 Weeks in Study CS-98-437

	Treatment Group		
	ADV 30 mg	ADV 10 mg	Placebo
Number of ITT patients	173	171	167
Number of patients with any SAEs	8 (5%)	9 (6%)	8 (5%)
Type of SAE			
ALT (SGPT) increase	0	1 (< 1%)[1]	1 (< 1%)[1]
AST (SGOT) increase	0	1 (< 1%)[1]	0
Abnormal liver function tests	0	1 (< 1%)[1]	0
Creatine kinase increase	0	1 (< 1%)	0
Fanconi-like syndrome	1 (< 1%)[1]	0	0
Chest pain	0	2 (1%)[1]	0
Abdominal pain	1 (< 1%)[1]	0	0
Accidental injury (whiplash)	0	1 (< 1%)	0
Inguinal hernia	1 (< 1%)	0	0
Viral infection (CMV infection)	0	0	1 (< 1%)
Coronary artery disorder	0	1 (< 1%)	1 (< 1%)
Myocardial infarct	1 (< 1%)[1]	0	1 (< 1%)
Hepatic hematoma	1 (< 1%)	0	0
Capillaritis	0	0	1 (< 1%)
Peripheral vascular disorder	0	0	1 (< 1%)
Vasovagal syncope	1 (< 1%)	0	0
Cholelithiasis	1 (< 1%)	0	0
Gastrointestinal hemorrhage	0	1 (< 1%)	0
Intestinal obstruction	0	0	1 (< 1%)
Rectal disorder (hemorrhoids)	1 (< 1%)	0	0
Weight loss (eating disorder)	0	1 (< 1%)	0
Neuropathy	0	0	1 (< 1%)
Hematuria	0	1 (< 1%)	0
Renal calculus	0	0	1 (< 1%)

[1] Considered possibly/probably related to study drug by the investigator
(Source: NDA 21-449, Volume 112, Table 39)

In the second 48 weeks of the study, two patients (1%) each in the placebo crossover to ADV 10 mg group and ADV 10 mg to ADV 10 mg group, three patients (4%) in the ADV 10 mg to placebo group, and five patients (4%) in the ADV 30 mg to placebo group reported serious adverse events. All of these events resulted in hospitalization. These are displayed in Table 8.2.1B.

Table 8.2.1B. Serious Adverse Events in the Second 48 Weeks in Study GS-98-437

	Treatment Group			
	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	ADV 30 mg to placebo[1]
Number of patients	138	85	70	142
Number of patients with SAE	2 (1%)	2 (1%)	3 (4%)	5 (4%)
Type of SAE				
Headache	0	0	1 (< 1%)	0
Abdominal pain	1 (< 1%)	0	0	1 (< 1%)
Confusion	0	0	1 (< 1%)	0
Depression	0	0	1 (< 1%)	0
Gastrointestinal hemorrhage	0	0	0	1 (< 1%)
Rectal hemorrhage	0	0	0	1 (< 1%)
Rash	1 (< 1%)	0	0	0
Urinary incontinence	0	1 (< 1%)[R]	0	0
Otitis media	1 (< 1%)	0	0	0
Pneumonia[2]	0	0	0	1 (< 1%)
Vogt Koyanagi Harada[2]	0	1 (< 1%)[R]	0	0
Hyperparathyroidism[2]	1 (< 1%)	0	0	0
Abnormal liver function tests	0	0	1 (< 1%)[R]	1 (< 1%)[R]

[R] Considered possibly/probably related to study drug by the investigator
[1] One patient (ID # 539-1132) who received ADV 30 mg daily in the first 48 weeks and ADV 10 mg daily (not placebo) in the second 48 weeks developed pneumonia.
[2] Serious adverse events reported after incorrect treatment assignment
(Source: NDA 21-449, Volume 131, Listing 21)

Case Review:

Of note are the following cases:

- Patient ID # 470-6075: A 48-year-old white female was enrolled and randomized to ADV 30 mg group in October 1999. In April 2000, routine laboratory tests revealed a phosphorus level of 1.6 mg/dL (normal range, 3.0-4.5 mg/dL). This was accompanied by a complaint of asthenia. Adefovir treatment was interrupted and the patient was hospitalized for supplemental phosphorus treatment. Serum creatinine also increased to 0.9 mg/dL from a baseline of 0.6 mg/dL. Subsequent work-up also showed aminoaciduria (glycine at 10 x ULN), and non-compensated respiratory academia consistent with Fanconi syndrome. She was also found to have concomitant vitamin D deficiency. By July 2000, the above abnormalities resolved. In August 2000, she was permanently discontinued from the study. The investigator assessed the Fanconi syndrome as related to study drug.

Reviewer's Comment

Fanconi-like syndrome has been reported to be associated with adefovir treatment in the HIV drug development program (please see section 8.5.3.1 for additional information).

- Patient ID # 0505-6018: A 41-year-old white male with family history of ischemic heart disease was enrolled in July 1999 and randomized to the ADV 30 mg group. In August 1999, the patient presented with a complaint of chest pain. A work-up including EKG was normal. Approximately two months later, he suffered an anterior myocardial infarction. Adefovir treatment was subsequently permanently discontinued. The investigator assessed the event as possibly related to study drug.

- Patient ID # 0505-6080: A 37-year-old white male was enrolled in October 1999 and randomized to the ADV 10 mg group. At the time, his ALT was 176 U/L and AST of 99 U/L. In December 1999, routine laboratory tests revealed an ALT of 796 U/L and AST of 333 U/L. The patient was asymptomatic, with no jaundice or other evidence of hepatic decompensation. Concerned that the elevated liver enzymes could pose "a threat to the well being of the patient," the investigator interrupted study drug. As the ALT and AST levels returned to baseline, study drug was restated in February 2000. However, the ALT and AST levels again increased to a peak of 668 U/L and 296 U/L, respectively, in April 2000. The study drug was permanently interrupted and the patient withdrew from the study in May 2000. In August, the patient's ALT and AST values were at a nadir of 24 U/L and 23 U/L, respectively.

- Patient ID # 381-1022: A 35-year-old Asian male was randomized in May 1999 to the ADV 10 mg group in the first 48 weeks of the study. In May 2000, he was re-randomized to receive placebo for the second 48 weeks. In early July 2000, the patient complained of flu-like symptoms and interrupted study drug on his own. A laboratory test revealed an ALT of 1,110 U/L (baseline level was 135 U/L). Adefovir treatment was interrupted. Follow-up laboratory tests revealed ALT of 2,155 U/L, AST 1,335 U/L, total bilirubin 3.9 mg/dL, albumin 3.8 g/dL, and prothrombin time 13.5 seconds. In mid July 2000, the patient was discontinued from the study and lamivudine therapy was started. In November 2000, liver function tests returned to normal: ALT was 43 U/L, AST 32 U/L, and total bilirubin 0.6 mg/dL.

Reviewer's comment

The hepatic event was probably related to an exacerbation of hepatitis associated with drug discontinuation.

- An 18-year-old Asian male was enrolled in August 1999 and randomized to ADV 30 mg group. In July 2000, he was re-randomized to receive placebo for the second 48 weeks of the study. At that time, his serum HBV DNA was 4.48 $\log_{10}$ copies/mL, ALT 68 U/L, and AST 38 U/L. In August 2000, his serum HBV DNA increased to 8.98 $\log_{10}$ copies/mL. In September 2000, the patient was found to have elevated ALT of 759 U/L and AST 224 U/L. The study drug (placebo) was interrupted. By October 2000, the ALT decreased to 392 U/L, and AST 123 U/L, and study drug (placebo) was restarted. In the next several months, the ALT levels remained in the 100's and AST 40's to 60's. The investigator considered the laboratory abnormalities as possibly related to study drug.

- A 29-year-old Asian male was enrolled in June 1999 and randomized to the ADV 10 mg group in the first 48 weeks of the study. In May 2000, he was re-randomized to receive adefovir 10 mg daily in the second 48 weeks. His serum HBV DNA remained less than 400 copies/mL, except for those measured in November 2000 (4.37 $\log_{10}$ copies/mL) and February 2001 (3.53 $\log_{10}$ copies/mL) when he received placebo due to error in treatment allocation. In mid February, the patient presented with constant headache, blurred vision and partial blindness in the left eye. Five days later, he experienced similar changes in the right eye. The study drug was discontinued. He was treated with steroid and lamivudine 100 mg daily. The treating ophthalmologist suspected Vogt-Koyanagi-Harada syndrome based on clinical presentation and patient's ethnicity. The patient was discontinued from the study. Subsequent follow-up visits did not show significant visual improvement, and he was not expected to regain vision completely. Although the investigator determined that the event was likely immune-mediated, he could not rule out a possible relationship to the study drug.

8.2.2. Study GS-98-438

A total of 4 patients (3%) in the ADV 10 mg group and 4 patients (7%) in the placebo group experienced serious adverse events in the first 48 weeks of the study. All patients except for the one with parotitis were hospitalized. None of these serious adverse events were considered related to study drug by the investigators. These are summarized in Table 8.2.2A. Serious adverse events occurring in the second 48 weeks of treatment are summarized in Table 8.2.2B.

Table 8.2.2A. Serious Adverse Events in the First 48 Weeks in Study GS-98-438

	Treatment Group	
	ADV 10 mg	Placebo
Number of ITT patients	123	61
Number of patients with any SAE	4(3%)	4(7%)
Type of SAE		
Post-liver biopsy pain	1 (< 1%)	0
Synovial fluid leakage (right hip)	0	1 (< 1%)
Dengue fever	1 (< 1%)	0
Transient ischemic attack	0	1 (< 1%)
Renal colic	1 (< 1%)	0
Sialadenitis	0	1 (< 1%)
Perianal abscess	1 (< 1%)	0

(Source: NDA 21-449, Volume 152, Listing 21)

Table 8.2.2B. Serious Adverse Events in the Second 48 Weeks in Study GS-98-438

	Treatment Group		
	ADV 10 mg to ADV 10 mg	ADV 10 mg to placebo	Placebo to ADV 10 mg
Number of ITT patients	79	40	60
Number with any SAE	1	1	3
Type of SAE			
Depression	0	1 (< 1%)	0
Cerebrovascular accident	1 (< 1%)	0	0
Renal colic	0	0	1 (< 1%)
Head injury	0	0	1 (< 1%)
Fracture (left femur)	0	0	1 (< 1%)

(Source: NDA 21-449, Volume 152, Listing 21)

8.2.3. Study GS-98-435

As of December 31, 2001, forty-nine patients (25%) in subcohort A (post-liver transplantation) reported serious adverse events. Eleven events in seven patients were assessed by the investigator as related to study drug. Among those of subcohort B (waitlisted for liver transplantation), 37 (29%) reported serious adverse events. Seven hepatic events in six patients were considered by the investigator as related to study drug.

Serious adverse events occurring in 2% of subcohort A patients are summarized in Table 8.2.3A, and those in subcohort B in Table 8.2.3B.