

2003

# Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis B

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From the New England Journal of Medicine, Marcellin, P., Chang, T-T., Lim, S.G., et al., Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis B, Vol. 348, Page 808, Copyright © 2003 Massachusetts Medical Society. Reprinted with permission.

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## ORIGINAL ARTICLE

# Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis B

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## ABSTRACT

**BACKGROUND**

In preclinical and phase 2 studies, adefovir dipivoxil demonstrated potent activity against hepatitis B virus (HBV), including lamivudine-resistant strains.

**METHODS**

We randomly assigned 515 patients with chronic hepatitis B who were positive for hepatitis B e antigen (HBeAg) to receive 10 mg of adefovir dipivoxil (172 patients), 30 mg of adefovir dipivoxil (173), or placebo (170) daily for 48 weeks. The primary end point was histologic improvement in the 10-mg group as compared with the placebo group.

**RESULTS**

After 48 weeks of treatment, significantly more patients who received 10 mg or 30 mg of adefovir dipivoxil per day than who received placebo had histologic improvement (53 percent [P<0.001], 59 percent [P<0.001], and 25 percent, respectively), a reduction in serum HBV DNA levels (by a median of 3.52 [P<0.001], 4.76 [P<0.001], and 0.55 log copies per milliliter, respectively), undetectable levels (fewer than 400 copies per milliliter) of serum HBV DNA (21 percent [P<0.001], 39 percent [P<0.001], and 0 percent, respectively), normalization of alanine aminotransferase levels (48 percent [P<0.001], 55 percent [P<0.001], and 16 percent, respectively), and HBeAg seroconversion (12 percent [P=0.049], 14 percent [P=0.01], and 6 percent, respectively). No adefovir-associated resistance mutations were identified in the HBV DNA polymerase gene. The safety profile of the 10-mg dose of adefovir dipivoxil was similar to that of placebo; however, there was a higher frequency of adverse events and renal laboratory abnormalities in the group given 30 mg of adefovir dipivoxil per day.

**CONCLUSIONS**

In patients with HBeAg-positive chronic hepatitis B, 48 weeks of 10 mg or 30 mg of adefovir dipivoxil per day resulted in histologic liver improvement, reduced serum HBV DNA and alanine aminotransferase levels, and increased the rates of HBeAg seroconversion. The 10-mg dose has a favorable risk–benefit profile for long-term treatment. No adefovir-associated resistance mutations were identified in the HBV DNA polymerase gene.

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N Engl J Med 2003;348:808-16.  
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**M**ORE THAN 350 MILLION PEOPLE worldwide have chronic hepatitis B virus (HBV) infection.<sup>1</sup> Effective treatments are required to prevent progression of chronic hepatitis B to cirrhosis, hepatocellular carcinoma, and death. Treatment with interferon alfa requires parenteral administration and can cause side effects, such as influenza-like symptoms, anorexia, and depression, that require an adjustment in the dose or discontinuation of therapy.<sup>2</sup> The risk of progressive liver damage decreases in patients who have hepatitis B e antigen (HBeAg) seroconversion after interferon therapy. Lamivudine suppresses HBV replication and improves histologic liver findings.<sup>3</sup> However, lamivudine resistance has been reported in up to 32 percent of patients after one year of therapy<sup>4</sup> and in 66 percent after four years.<sup>5</sup> Some patients with lamivudine resistance have had a severe exacerbation of hepatitis and progressive liver disease.<sup>6</sup> Therefore, well-tolerated antiviral agents that provide clinical benefit without inducing resistance are needed to manage chronic hepatitis B.

Adefovir dipivoxil (Hepsera, Gilead Sciences) is an oral prodrug of adefovir, an analogue of adenosine monophosphate. The active intracellular metabolite, adefovir diphosphate, inhibits HBV DNA polymerase at levels much lower than those needed to inhibit human DNA polymerases. In phase 2 studies, daily doses of 30 mg and 60 mg of adefovir dipivoxil inhibited HBV replication, reducing serum HBV DNA by approximately 4 log copies per milliliter after 12 weeks.<sup>7</sup> Adefovir dipivoxil has also been efficacious in patients with lamivudine-resistant HBV.<sup>8</sup>

We elected to evaluate in a double-blind, placebo-controlled study the effects of 10-mg and 30-mg doses of adefovir dipivoxil in patients with HBeAg-positive chronic hepatitis B on the basis of the results of phase 2 studies, which showed that the antiviral activity of doses greater than or equal to 30 mg was similar. During the long-term, phase 2 study, data indicated that the 30-mg dose was associated with mild, reversible nephrotoxicity after 32 weeks. Therefore, we amended the primary end point for this study before the analysis and unblinding, to compare a 10-mg dose of adefovir dipivoxil with placebo. We report the 48-week results, but the study is ongoing and will continue for up to 5 years. When the study was designed, lamivudine was still an investigational agent; therefore, placebo was selected as the control.

## METHODS

### STUDY DESIGN

From March 1999 to March 2000, patients were recruited from 78 centers in North America, Europe, Australia, and Southeast Asia and randomly assigned in a 1:1:1 ratio to receive 10 mg of adefovir dipivoxil per day, 30 mg of adefovir dipivoxil per day, or placebo. The central randomization scheme was stratified according to seven geographic regions. Permuted blocks (with a block size of six) were used in each stratum. The placebo and adefovir dipivoxil tablets were formulated to be indistinguishable from one another in appearance and taste.

The study was conducted in compliance with the Declaration of Helsinki and approved by appropriate local regulatory bodies. All patients provided written informed consent. Liver biopsy was performed at base line and week 48. Biopsy specimens obtained within six months before randomization could be used if they had been obtained more than six months after the completion of prior hepatitis B therapy. Patients were evaluated every four weeks.

Clinical data were collected, monitored, and entered into a data base by Quintiles. Laboratory tests were conducted by Covance. The sponsor held the data and conducted the statistical analyses, which were predefined; the academic investigators had full access to the data and contributed substantially to the design of the study, the collection of the data, the analysis and interpretation of the data, and the drafting of the manuscript. All authors approved the final draft of the manuscript.

### PATIENTS

Male and female patients 16 to 65 years of age who had hepatitis B e antigen–positive chronic hepatitis B and compensated liver disease were eligible for the study. Chronic hepatitis B was defined by the presence of serum hepatitis B surface antigen for at least six months, a serum HBV DNA level of at least 1 million copies per milliliter (measured with the Roche Amplicor Monitor polymerase-chain-reaction [PCR] assay), and a serum alanine aminotransferase level that was 1.2 to 10 times the upper limit of the normal range. Patients were required to have a prothrombin time that was no more than one second above the normal range, a serum albumin level of at least 3 g per deciliter, a total bilirubin level of no more than 2.5 mg per deciliter (43  $\mu$ mol per liter), a serum creatinine level of no more than 1.5 mg

per deciliter (133  $\mu\text{mol}$  per liter), and an adequate blood count. Women of childbearing potential were eligible if they had a negative pregnancy test and were using effective contraception.

Criteria for exclusion included a coexisting serious medical or psychiatric illness; immune globulin, interferon, or other immune- or cytokine-based therapies with possible activity against HBV disease within 6 months before screening; organ or bone marrow transplantation; recent treatment with systemic corticosteroids, immunosuppressants, or chemotherapeutic agents; a serum alpha-fetoprotein level of at least 50 ng per milliliter; evidence of a hepatic mass; liver disease that was not due to hepatitis B; prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV; and seropositivity for human immunodeficiency virus or hepatitis C or D virus.

#### END POINTS

The primary efficacy end point was histologic improvement, defined as a reduction of at least two points in the Knodell necroinflammatory score with no concurrent worsening of the Knodell fibrosis score 48 weeks after base line.<sup>9</sup> The liver-biopsy specimens were evaluated by an independent histopathologist who was unaware of the patients' treatment assignments or of the timing of liver biopsy. Ranked assessments of necroinflammatory activity and fibrosis were also performed (and scored as improved, no change, or worse).

Secondary end points included the change from base line in serum HBV DNA levels, the proportion of patients with undetectable levels of HBV DNA, the effect of treatment on the alanine aminotransferase level, and the proportion of patients with loss or seroconversion of HBeAg. Serum HBV DNA levels were measured by the Roche Amplicor HBV Monitor PCR assay (lower limit of detection, 400 copies per milliliter), and the values were log-transformed with use of a base 10 scale.

#### SAFETY ANALYSIS

The primary safety analysis included all patients who received at least one dose of study medication and all events that occurred during treatment or within 30 days after the discontinuation of study drug. The severity of adverse events and laboratory abnormalities was graded according to the Common Toxicity Criteria of the National Institute of Allergy and Infectious Diseases.<sup>10</sup>

#### DETECTION OF HBV POLYMERASE MUTATIONS

All serum samples obtained at base line and week 48 were examined in a blinded fashion. HBV DNA was isolated and amplified by PCR. The positive and negative strands of the HBV polymerase gene spanning the polymerase–reverse-transcriptase domain (amino acids 349 to 692) were sequenced. The HBV sequences of the samples obtained at base line and week 48 from the same patient were aligned with the MegAlign program (DNASStar).

#### STATISTICAL ANALYSIS

The study was designed to enroll 166 patients per group, with 90 percent power to detect an absolute difference of 20 percent (50 percent vs. 30 percent) between the group given 10 mg of adefovir dipivoxil and the placebo group, assuming that 25 percent of patients would have missing biopsy specimens that would be considered treatment failures and that 8 percent of patients would have missing base-line biopsy specimens, on the basis of a two-sided type I error rate of 0.05. The study had 79 percent power to detect an absolute difference of 10 percent (16 percent vs. 6 percent) in the rate of seroconversion between the group given 10 mg of adefovir dipivoxil and the placebo group, assuming that 10 percent of patients would have missing values (which were counted as treatment failures). Patients who received at least one dose of study medication were included in the analyses. Patients with missing or unassessable base-line liver-biopsy specimens were prospectively excluded from the primary efficacy analysis. Patients with missing or unassessable data at 48 weeks were considered not to have had responses. The unstratified Cochran–Mantel–Haenszel test was used to compare each of the adefovir dipivoxil groups with the placebo group. All P values were two-sided. No adjustments were made for multiple comparisons. All serum HBV DNA results below the lower limit of detection (less than 400 copies per milliliter) were analyzed as being 400 copies per milliliter. No interim analyses were performed other than safety-data summaries, which were prepared every six months for a review by the independent external data-monitoring committee.

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## RESULTS

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#### CHARACTERISTICS OF THE PATIENTS

Among the 515 patients who were enrolled, 172 were randomly assigned to receive 10 mg of adef-

ovir dipivoxil per day, 173 to receive 30 mg per day, and 170 to receive placebo. Four patients took no study medication (one in the 10-mg group and three in the placebo group). Of the remaining 511 patients, base-line biopsy specimens were available for 168 patients in the 10-mg group, 165 in the 30-mg group, and 161 in the placebo group. There were no significant differences in demographic or HBV disease characteristics (Table 1) or previous anti-HBV treatments among the groups. A total of 123 patients (24 percent) had received treatment with interferon alfa.

#### HISTOLOGIC RESPONSE

The primary analysis was based on the 329 patients (97 percent) in the group given 10 mg of adefovir dipivoxil and the placebo group for whom base-line liver-biopsy specimens were available. Histologic improvement was seen in 53 percent of patients in the group given 10 mg of adefovir dipivoxil, 25 percent of those in the placebo group ( $P<0.001$ ) (Table 2), and 59 percent of those in the group given 30 mg of adefovir dipivoxil ( $P<0.001$ ). The results were not changed by the addition of the four patients who underwent randomization but who did not take any study medication.

After 48 weeks, patients who received 10 mg of adefovir dipivoxil per day had a median reduction in the Knodell necroinflammatory score of two points and those who received 30 mg per day had a median reduction of three points, as compared with no change in the placebo group ( $P<0.001$  for both comparisons) (Table 2). On ranked assessment, higher percentages of patients in the 10-mg group and the 30-mg group than in the placebo group had improvements in necroinflammatory activity and fibrosis, and a higher percentage of patients in the placebo group had worsening of necroinflammatory activity and fibrosis ( $P<0.001$  for each comparison).

#### VIROLOGIC RESPONSE

At week 48, serum HBV DNA levels had decreased by a median of 3.52 log copies per milliliter in the group given 10 mg of adefovir dipivoxil and 4.76 log copies per milliliter in the 30-mg group, as compared with 0.55 log copies per milliliter in the placebo group ( $P<0.001$  for each comparison) (Table 3 and Fig. 1). Twenty-one percent of the patients in the 10-mg group and 39 percent of those in the 30-mg group had undetectable serum levels of HBV DNA, as compared with 0 percent of the patients in the

**Table 1. Base-Line Characteristics of the Patients.\***

Characteristic	Placebo (N=167)	10 mg of Adefovir Dipivoxil (N=171)	30 mg of Adefovir Dipivoxil (N=173)
Age — yr			
Mean $\pm$ SD	37 $\pm$ 11.8	34 $\pm$ 11.2	34 $\pm$ 10.8
Median	35	32	32
Range	16–66	16–65	17–68
Male sex — no. (%)	119 (71)	130 (76)	129 (75)
Race or ethnic group — no. (%)			
White	60 (36)	60 (35)	64 (37)
Black	3 (2)	8 (5)	5 (3)
Asian	101 (60)	102 (60)	101 (58)
Other	3 (2)	1 (1)	3 (2)
Weight — kg			
Mean $\pm$ SD	70 $\pm$ 14.9	72 $\pm$ 15.9	69 $\pm$ 15.9
Median	70	71	67
Range	41–134	43–118	40–129
Alanine aminotransferase			
Mean $\pm$ SD — U/liter	139 $\pm$ 131	139 $\pm$ 154	124 $\pm$ 96
Median — U/liter	94	95	92
$\leq$ ULN — no. (%)	3 (2)	3 (2)	4 (2)
$>$ ULN — no. (%)	164 (98)	168 (98)	169 (98)
Multiples of ULN			
Mean $\pm$ SD	3.4 $\pm$ 3.1	3.4 $\pm$ 4.0	3.0 $\pm$ 2.3
Median	2.4	2.3	2.3
HBV DNA — log copies/ml†			
Mean $\pm$ SD	8.12 $\pm$ 0.89	8.25 $\pm$ 0.90	8.22 $\pm$ 0.84
Median	8.33	8.40	8.34
Total Knodell score			
Mean $\pm$ SD	9.65 $\pm$ 3.45	9.01 $\pm$ 3.33	9.55 $\pm$ 3.33
Median	10.0	9.5	10.0
Range	1–17	0–17	0–16
Knodell necroinflammatory score			
Mean $\pm$ SD	7.83 $\pm$ 2.89	7.37 $\pm$ 2.75	7.84 $\pm$ 2.82
Median	8.0	7.0	8.0
Range	1–14	0–14	0–12
Knodell fibrosis score			
Mean $\pm$ SD	1.83 $\pm$ 1.12	1.64 $\pm$ 1.09	1.71 $\pm$ 1.06
Median	1.0	1.0	1.0
Range	0–4	0–4	0–4

\* ULN denotes upper limit of the normal range, and HBV hepatitis B virus.

† Values were log-transformed with use of a base 10 scale.

placebo group ( $P<0.001$  for each comparison). Loss of HBeAg occurred in 24 percent of the patients in the 10-mg group and 27 percent of those in the 30-mg group, as compared with 11 percent of the patients in the placebo group ( $P<0.001$  for each comparison). HBeAg seroconversion occurred in 12 percent of the patients in the 10-mg group and 14 percent of those in the 30-mg group, as compared



**Table 2. Histologic Improvement and Changes in Necroinflammatory Activity and Fibrosis from Base Line to Week 48.\***

Variable	Placebo	10 mg of Adefovir Dipivoxil	30 mg of Adefovir Dipivoxil
<b>Histologic improvement†</b>			
No. of patients‡	161	168	165
Histologic improvement — no. (%)	41 (25)	89 (53)	98 (59)
No improvement — no. (%)	105 (65)	61 (36)	47 (28)
Missing data — no. (%)	14 (9)	16 (10)	16 (10)
Unassessable data — no. (%)	1 (1)	2 (1)	4 (2)
Unstratified relative risk		2.1	2.3
95% CI		1.5 to 2.8	1.7 to 3.1
P value		<0.001	<0.001
Stratum-adjusted relative risk		2.1	2.3
95% CI§		1.6 to 2.8	1.7 to 3.1
P value		<0.001	<0.001
<b>Necroinflammatory activity</b>			
<b>Knodell score</b>			
No. of patients¶	146	150	145
Mean (±SD) change in score	-0.16±3.06	-2.58±3.22	-3.17±3.30
Median change in score	0	-2	-3
Range of scores	-10 to 7	-9 to 6	-9 to 5
P value		<0.001	<0.001
<b>Ranked assessment</b>			
No. of patients¶	145	150	145
Improved — no. (%)	59 (41)	107 (71)	112 (77)
No change — no. (%)	37 (26)	23 (15)	18 (12)
Worse — no. (%)	49 (34)	20 (13)	15 (10)
P value		<0.001	<0.001
<b>Fibrosis</b>			
<b>Knodell score</b>			
No. of patients¶	146	150	145
Mean (±SD) change in score	-0.01±0.86	-0.18±0.84	-0.32±0.80
Median change in score	0	0	0
Range of scores	-3 to 2	-2 to 2	-2 to 2
P value		0.061	0.001
<b>Ranked assessment</b>			
No. of patients¶	145	150	145
Improved — no. (%)	35 (24)	62 (41)	78 (54)
No change — no. (%)	72 (50)	67 (45)	53 (37)
Worse — no. (%)	38 (26)	21 (14)	14 (10)
P value		<0.001	<0.001

\* Relative risks and P values are for the comparison with the placebo group. CI denotes confidence interval.  
 † Histologic improvement was defined as a decrease of at least two points in the Knodell necroinflammatory score from base line to week 48, with no concurrent worsening of the Knodell fibrosis score. Patients who did not satisfy this definition were considered not to have histologic improvement. Patients with missing or unassessable data at week 48 were considered not to have had histologic improvement in the comparison between each adefovir dipivoxil group and the placebo group.  
 ‡ The number of patients is the number with assessable liver-biopsy specimens at base line.  
 § Values were adjusted for the seven geographic regions involved in the study (Europe, the United States, Canada, Australia, Taiwan, Thailand, and other parts of Asia [Singapore, the Philippines, and Malaysia]).  
 ¶ The number of patients is the number with assessable liver-biopsy specimens at base line and week 48.  
 || P values are from the general-association Cochran–Mantel–Haenszel statistic for comparisons of the 10-mg group or the 30-mg group with the placebo group. All P values are two-sided at a significance level of 0.05, with no adjustments for multiple comparisons.

with 6 percent of the patients in the placebo group (P=0.049 and P=0.011, respectively).

**BIOCHEMICAL RESPONSE**

Median reductions in serum alanine aminotransferase levels at week 48 were 51 IU per liter in the 10-mg group and 54 IU per liter in the 30-mg group, as compared with 17 IU per liter in the placebo group (P<0.001 for each comparison) (Table 3). Forty-eight percent of the patients who received 10 mg of adefovir dipivoxil per day and 55 percent of those who received 30 mg per day had normal alanine aminotransferase values at week 48, as compared with 16 percent of those who received placebo (P<0.001 for both comparisons).

**RESISTANCE PROFILE**

The polymerase–reverse transcriptase domain of the HBV polymerase gene was sequenced from serum samples obtained at base line and week 48 in 381 patients with detectable serum HBV DNA at both times. No mutations occurred at higher than background frequencies (less than 1.6 percent). Seven different novel substitutions were found at conserved sites in the HBV polymerase in seven patients (four of whom received adefovir dipivoxil and three of whom received placebo). All four of the patients who received adefovir dipivoxil had significant reductions in serum HBV DNA levels at week 48. In vitro phenotypic analyses demonstrated that viruses containing any of the seven substitutions remained fully susceptible to adefovir.

**SAFETY**

Similar percentages of patients in each group discontinued the study prematurely: 7 percent of those given 10 mg of adefovir dipivoxil per day and 8 percent of those given 30 mg per day and those given placebo. The incidence of severe (grade 3 or 4) clinical adverse events was similar: 10 percent in patients who received 10 mg of adefovir dipivoxil per day, 9 percent in those who received 30 mg per day, and 8 percent in the placebo group. The safety profile of the 10-mg group was similar to that of placebo with respect to all reported adverse events except asthenia (25 percent in the 10-mg group vs. 19 percent in the placebo group) and diarrhea (13 percent vs. 8 percent) (Table 4). Anorexia (10 percent) and pharyngitis (40 percent) occurred more frequently in the 30-mg group. Adverse events leading to the discontinuation of the study drug occurred in 2 percent of the patients in the 10-mg group, 3 percent of

**Table 3. Virologic and Biochemical Responses at Week 48.\***

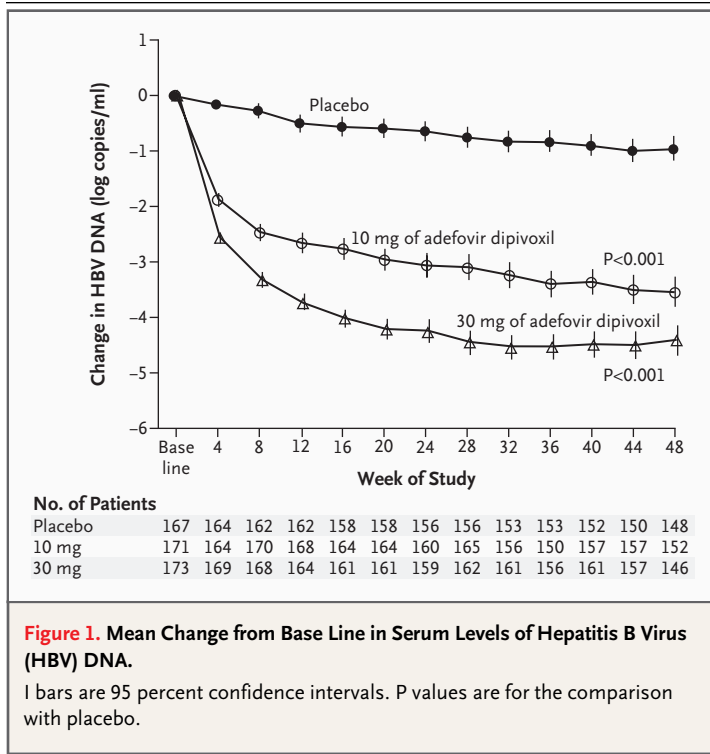
Variable	Placebo (N=167)	10 mg of Adefovir Dipivoxil (N=171)	30 mg of Adefovir Dipivoxil (N=173)
<b>Virologic response</b>			
Change in serum HBV DNA — log copies/ml			
Mean ±SD	-0.98±1.32	-3.57±1.64	-4.45±1.62
Median	-0.55	-3.52	-4.76
95% CI	-1.20 to -0.77	-3.84 to -3.31	-4.72 to -4.19
P value		<0.001	<0.001
Serum HBV DNA <400 copies/ml — no. (%)	0	36 (21)	67 (39)
P value†		<0.001	<0.001
HBeAg seroconversion — no./total no. (%)‡§	9/161 (6)	20/171 (12)	23/165 (14)
P value†		<0.049	<0.011
HBeAg loss — no./total no. (%)‡	17/161 (11)	41/171 (24)	44/165 (27)
P value†		<0.001	<0.001
<b>Biochemical response</b>			
Change in serum alanine aminotransferase level — IU/liter			
Mean ±SD	-23.0±140.7	-92.1±167.2	-74.4±128.4
Median	-17	-51	-54
95% CI	-45.9 to -0.2	-118.8 to -65.3	-95.6 to -53.3
P value		<0.001	<0.001
Normalization of alanine aminotransferase — no./total no. (%)¶	26/164 (16)	81/168 (48)	93/169 (55)
P value†		<0.001	<0.001

\* HBV denotes hepatitis B virus, and CI confidence interval.  
 † P values are from the general-association Cochran–Mantel–Haenszel statistic for comparisons of each adefovir dipivoxil group with the placebo group. All P values are two-sided at a significance level of 0.05, with no adjustments for multiple comparisons.  
 ‡ Patients who were positive for hepatitis B e antigen (HBeAg) at base line were included in the analysis.  
 § Seroconversion was defined as loss of HBeAg and concurrent gain of antibody against HBeAg at 48 weeks.  
 ¶ Patients with base-line alanine aminotransferase levels that exceeded the upper limit of the normal range were included in the analysis.

those in the 30-mg group, and less than 1 percent of those in the placebo group. These events included increased alanine aminotransferase or aspartate aminotransferase levels, weight loss, and rash in the 10-mg group; nausea, abdominal pain, headache, Fanconi-like syndrome, amblyopia, and myocardial infarction in the 30-mg group; and nausea in the placebo group.

There was no significant change in median serum creatinine levels at week 48 in the 10-mg group





and the placebo group; the 30-mg group had a median increase of 0.2 mg per deciliter (18  $\mu$ mol per liter). There were no increases from base line of 0.5 mg per deciliter (44  $\mu$ mol per liter) or greater in the serum creatinine level (confirmed by two consecutive laboratory assessments) in the 10-mg group or the placebo group, but 8 percent of patients in the 30-mg group had such an increase ( $P<0.001$ ). In all cases, renal function normalized with a dose reduction or an interruption of treatment. The maximal reported serum creatinine level was 1.8 mg per deciliter (159  $\mu$ mol per liter) in a patient in the 30-mg group. There was a median increase in serum phosphorus of 0.1 mg per deciliter (0.03 mmol per liter) in the 10-mg group and the placebo group and a median decrease of 0.1 mg per deciliter in the 30-mg group. There were no confirmed instances of serum phosphorus levels below 2.0 mg per deciliter (0.65 mmol per liter). The incidence of grade 3 or 4 laboratory abnormalities was similar in the adefovir dipivoxil and placebo groups, except that aspartate aminotransferase and alanine aminotransferase levels were higher in the placebo group.

Increases in alanine aminotransferase levels to more than 10 times the upper limit of the normal range occurred in 10 percent of patients in the group given 10 mg of adefovir dipivoxil per day, 8 percent of those given 30 mg per day, and 19 percent of those given placebo. Concurrent changes in total bilirubin levels, serum albumin levels, or the prothrombin time were not seen in any patient in the 10-mg or 30-mg group. In the placebo group, one patient had a concurrent increase in the total bilirubin level to greater than 2.5 mg per deciliter and to at least 1 mg per deciliter (17.1  $\mu$ mol per liter) above the base-line value, and one had a concurrent decrease in the serum albumin level (to less than 3.0 g per liter).

After week 48, all patients were reassigned to new treatment groups for the second 48 weeks of the study. All patients in the placebo group received 10 mg of adefovir dipivoxil per day. Patients in the 10-mg group were randomly assigned to receive either continued treatment with 10 mg per day or placebo. All patients in the 30-mg group received placebo.

An interim analysis of data from the second 48-week period showed a continued antiviral, serologic, and biochemical response in patients who continued to receive 10 mg of adefovir dipivoxil per day (median duration of additional therapy, 16 weeks). By week 72, 46 percent of patients had fewer than 400 copies of serum HBV DNA per milliliter, 75 per-

**Table 4. Adverse Events Reported by at Least 10 Percent of Patients in the Group Given 30 mg of Adefovir Dipivoxil per Day.**

Adverse Event	Placebo	10 mg of	30 mg of
	(N=167)	Adefovir Dipivoxil (N=171)	Adefovir Dipivoxil (N=173)
<i>number of patients (percent)</i>			
Body as a whole			
Headache	37 (22)	43 (25)	45 (26)
Asthenia	32 (19)	42 (25)	45 (26)
Abdominal pain	32 (19)	31 (18)	38 (22)
Flu-like syndrome	31 (19)	28 (16)	32 (18)
Pain	21 (13)	19 (11)	13 (8)
Back pain	11 (7)	11 (6)	17 (10)
Digestive tract			
Nausea	23 (14)	17 (10)	31 (18)
Diarrhea	13 (8)	23 (13)	25 (14)
Dyspepsia	14 (8)	15 (9)	19 (11)
Flatulence	10 (6)	13 (8)	18 (10)
Anorexia	9 (5)	6 (4)	18 (10)
Nervous system			
Dizziness	13 (8)	9 (5)	18 (10)
Respiratory tract			
Pharyngitis	54 (32)	44 (26)	70 (40)
Increased cough	21 (13)	11 (6)	19 (11)

cent had normalization of alanine aminotransferase levels, 44 percent had loss of HBeAg, and 23 percent had HBeAg seroconversion. Safety data from the second 48-week period were similar to those in the first 48 weeks.

## DISCUSSION

In patients with chronic hepatitis B, 48 weeks of treatment with adefovir dipivoxil resulted in significant histologic improvement, reduced serum HBV DNA levels, and increased normalization of alanine aminotransferase levels and HBeAg seroconversion, as compared with placebo. These results are similar to those in the 52-week pivotal clinical trials of lamivudine.<sup>3,4</sup> Lai et al. reported significant histologic improvement in 56 percent of patients after one year of treatment with lamivudine, although the development of serum HBV DNA polymerase mutations was associated with increases in alanine aminotransferase and HBV DNA.<sup>3</sup> Dienstag et al. reported histologic improvement in 52 percent of patients who received 100 mg of lamivudine per day; anti-HBeAg antibodies developed in 17 percent, and 32 percent lost serum HBeAg.<sup>4</sup>

The patients in this study were from North America, Europe, Australia, and Southeast Asia; the majority were Asian. The two pivotal trials of lamivudine included predominantly white patients in the United States<sup>4</sup> or only Chinese patients.<sup>3</sup> Several studies have found regional and ethnic differences in response to both HBV infection and treatments for hepatitis B.<sup>11</sup> The histologic improvement in our

patients was similar among the geographic regions; therefore, our results may be more representative of the global population of patients with chronic hepatitis B. However, black patients were not well represented.

The efficacy profile of the 10-mg and 30-mg doses of adefovir dipivoxil was similar, except for differences in the magnitude of the decrease in serum HBV DNA levels and the percentage of patients with undetectable serum HBV DNA levels at 48 weeks. Both doses were well tolerated. However, the increases in serum creatinine levels in the 30-mg group limit the long-term use of this dose and instead favor the 10-mg dose. No adefovir-associated resistance mutations were identified during 48 weeks of treatment, which is consistent with findings from other studies evaluating up to 60 weeks of treatment.<sup>12,13</sup>

In our study, treatment with 10 mg of adefovir dipivoxil daily was well tolerated and significantly improved histologic findings in the liver, reduced serum HBV DNA levels, normalized alanine aminotransferase levels, and induced HBeAg loss and seroconversion in a diverse population. The favorable resistance profile of adefovir dipivoxil during 48 weeks of therapy is an advantage, since many patients with chronic hepatitis B require long-term therapy.

Supported by Gilead Sciences.

Drs. Wulfsohn, Xiong, and Brosgart and Mr. Fry are employees of Gilead Sciences and report equity ownership in Gilead Sciences. Drs. Marcellin, Tong, and Goodman report having served as consultants to Gilead Sciences. Dr. Marcellin reports having served as a paid lecturer for Gilead Sciences.

## APPENDIX

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## REFERENCES

- Hepatitis B. Fact sheet WHO/204. Geneva: World Health Organization, October 2000. (Accessed January 7, 2003, at <http://www.who.int/inf-fs/en/fact204.htm>.)
- Intron A. Kenilworth, N.J.: Schering, 2001 (package insert).
- Lai C-L, Chien R-N, Leung NWY, et al. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61-8.
- Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256-63.
- Leung NW, Lai C-L, Guan R, Liaw Y-F. The effect of longer duration of harbouring lamivudine-resistant hepatitis B virus (YMDD mutants) on liver histology during 3 years lamivudine therapy in Chinese patients. *Hepatology* 2001;34:348A. abstract.
- Kim JW, Lee HS, Woo GH, et al. Fatal submassive hepatic necrosis associated with tyrosine-methionine-aspartate-aspartate-motif mutation of hepatitis B virus after long-term lamivudine therapy. *Clin Infect Dis* 2001;33:403-5.
- Heathcote EJ, Jeffers L, Wright T, et al. Loss of serum HBV DNA and HBeAg and seroconversion following short-term (12 weeks) adefovir dipivoxil therapy in chronic hepatitis B: two placebo-controlled phase II studies. *Hepatology* 1998;28:Suppl:317A. abstract.
- Schiff ER, Neuhaus P, Tillman H, et al. Safety and efficacy of adefovir dipivoxil for the treatment of lamivudine resistant HBV in patients post liver transplantation. *Hepatology* 2001;34:446A. abstract.
- Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431-5.
- Common toxicity criteria, version 2. Bethesda, Md.: National Cancer Institute, 1999. (Accessed February 4, 2003, at <http://ctep.info.nih.gov>.)
- Chien R-N, Liaw Y-F, Atkins M. Pretherapy alanine transaminase level as a determinant of hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 1999;30:770-4.
- Yang H, Westland CE, Delaney WE IV, et al. Resistance surveillance in chronic hepatitis B patients treated with adefovir dipivoxil for up to 60 weeks. *Hepatology* 2002;36:464-73.
- Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* 2001;358:718-23.

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