



FINAL CLINICAL STUDY REPORT

Study Title: A Multi-center Phase 3, Open-Label, Parallel-Group Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Adefovir Dipivoxil Liquid Suspension in Patients with Chronic Hepatitis B and Varying Degrees of Renal Impairment

Name of Test Drug: Adefovir Dipivoxil

Indication: Chronic Hepatitis B

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study No.: GS-02-526

Phase of Development: Phase 3

IND No.: 52,182

EudraCT No.: N/A

Study Start Date: 13 June 2003 (First Subject Screened)

Study End Date: 13 March 2006 (Last Subject Observation)

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Report Date: 27 November 2006

Previous Report Date(s): None

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Multi-center Phase 3, Open-Label, Parallel-Group Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Adefovir Dipivoxil Liquid Suspension in Patients with Chronic Hepatitis B and Varying Degrees of Renal Impairment

Investigators: Multicenter

Study Centers: Eight centers (two centers in the US, four centers in France, and two centers in Germany) enrolled subjects.

Publications: None.

Study Period:

13 June 2003 (First subject screened)
13 March 2006 (Last subject observation)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To evaluate the efficacy of adefovir dipivoxil when administered as an oral liquid suspension once daily to subjects with chronic hepatitis B and mild, moderate, severe, or end-stage renal impairment, including subjects on hemodialysis.

The secondary objectives of this study were as follows:

- To evaluate the safety of adefovir dipivoxil oral liquid suspension in subjects with chronic hepatitis B and mild, moderate, severe, or end-stage renal impairment, including subjects on hemodialysis.
- To evaluate adefovir pharmacokinetic parameters at baseline and at Week 12 in all treatment groups, and at Week 48 in Groups 1, 2, 3, and 4A only.

STUDY SYNOPSIS (CONTINUED)

Methodology: In this multicenter, phase 3, open-label, parallel-group study, subjects with chronic hepatitis B were stratified into treatment groups based on their calculated creatinine clearance (CL_{cr}) (using the Cockcroft-Gault formula) at screening: mild (Group 1), moderate (Group 2), severe (Group 3) renal impairment, and end-stage renal disease (ESRD) without hemodialysis (Group 4A). Group 4B comprised subjects who required hemodialysis, regardless of creatinine clearance.

Study Group	Category of Renal Impairment	Calculated CL_{cr} at Screening	On Hemodialysis	Study Treatment Dose
1	Mild	≥ 50 to < 80 mL/min	No	10 mg/day
2	Moderate	≥ 20 to < 50 mL/min	No	5 mg/day
3	Severe	≥ 10 to < 20 mL/min	No	2.5 mg/day
4A	End-stage Renal Disease	< 10 mL/min, no hemodialysis	No	1.0 mg/day
4B	End-stage Renal Disease	Any calculated CL_{cr} value	Yes	1.0 mg (first dose); thereafter 0.5 mg after each dialysis (3 times per week)

All subjects were treated with adefovir dipivoxil oral suspension according to the doses shown in the table above. Subjects in Groups 1-4A were treated for up to 48 weeks, and subjects in Group 4B were treated for up to 12 weeks. All subjects were to return for post-treatment follow-up visits for 16 weeks after either completing the study or early study discontinuation, unless they remained on adefovir dipivoxil treatment.

Study assessments were performed at clinic visits every 4 weeks in the treatment and follow-up periods.

Number of Subjects (Planned and Analyzed):

Planned: 48 total, 12 each into mild, moderate, and severe renal impairment groups, and 12 into ESRD treatment group.

Randomized: 28 total, 10 mild, 12 moderate, and 2 severe renal impairment, and 4 ESRD with hemodialysis subjects.

Evaluable: Efficacy: 28 subjects
Pharmacokinetics: 27 subjects
Safety: 28 subjects

STUDY SYNOPSIS (CONTINUED)

Diagnosis and Main Criteria for Inclusion: Adult subjects with chronic hepatitis B and mild, moderate, or severe renal impairment, or end-stage renal disease (ESRD). Positive HBsAg test for ≥ 6 months and at screening and positive serum HBV DNA ($\geq 10^5$ copies/mL) at screening. Subjects were required to have ESRD or to have renal impairment (calculated $CL_{cr} < 80$ mL/min) that was stable (at least three measurements obtained over a ≥ 12 -week period prior to study entry and including the screening value, with the lowest and highest measurement falling within 20% of the screening calculated CL_{cr} value).

Duration of Treatment: The planned duration of treatment for subjects in Groups 1–4A was 48 weeks and in Group 4B was 12 weeks. The actual (median) duration of treatment was 48.0, 48.1, and 24.6 weeks in Groups 1, 2, and 3, respectively. No subjects were enrolled in Group 4A. In Group 4B, the actual (median) duration of treatment was 13.4 weeks.

Test Product, Dose, Mode of Administration, and Batch No.:

Adefovir dipivoxil up to 10 mg daily (based on treatment group), oral liquid suspension Development formulation (Lot number: U201A1) dispensed at all study visits through August 2004.

Modified formulation (Lot numbers: U302A1, U401A1) dispensed at all study visits starting after August 2004.

Reference Therapy, Dose, Mode of Administration, and Batch No.: None.

Criteria for Evaluation:

Efficacy: Serum HBV DNA concentration, serum ALT concentration, and serology endpoints (HBeAg loss, HBeAg seroconversion, HBsAg loss, HBsAg seroconversion).

Pharmacokinetics: The following adefovir pharmacokinetic parameters were estimated for subjects in Groups 1, 2, 3, and 4A: C_{max} , T_{max} , C_{last} , T_{last} , C_{tau} , λ_z , AUC_{0-last} , AUC_{inf} , AUC_{tau} , $\%AUC_{exp}$, $T_{1/2}$, CL/F , V_z/F , A_e , $\%Dose_{excreted}$, CL_r , and CL_{cr} . The following adefovir pharmacokinetic parameters were estimated for subjects in Group 4B: C_{max} , T_{max} , $C_{predose}$, $C_{predialysis}$, $C_{postdialysis}$, and AUC_{0-24} .

Safety: Adverse events, clinical laboratory test findings, vital sign results, use of concomitant medications, and discontinuations of study medication.

STUDY SYNOPSIS (CONTINUED)

Statistical Methods:

Efficacy: Efficacy measures were analyzed in the modified intent-to-treat population—the set of subjects who received at least one dose of study medication, and who were HBsAg+ with a calculated CL_{cr} of less than 80 mL/min at study screening. The primary efficacy analysis assessed the noninferiority of adefovir dipivoxil liquid suspension at the dose levels in this study (10 mg, 5 mg, 2.5 mg, 1 mg, and 1 mg followed by 0.5 mg post dialysis) relative to the historical results observed in Studies GS-98-437 and GS-98-438 for adefovir dipivoxil 10 mg tablet formulation. A two-sided 90% confidence interval for the time-weighted average change in serum HBV DNA concentrations from baseline to Week 12 ($DAVG_{12}$) was constructed. A dosing regimen utilizing adefovir dipivoxil liquid suspension in subjects with renal impairment was to be declared noninferior to adefovir dipivoxil 10 mg tablets dosed once daily if the upper limit of the 90% confidence interval for $DAVG_{12}$ was less than $-1.5 \log_{10}$ copies/mL.

Secondary efficacy analyses included summary statistics for change from baseline in serum HBV DNA and ALT concentrations by visit, and numbers and percentages of subjects with serum HBV DNA levels < 1000 copies/mL (for subjects with HBV DNA \geq 1000 copies/mL at baseline), ALT normalization (for subjects with ALT > ULN at baseline), HBeAg loss and HBeAg seroconversion (for subjects with HBeAg+ or borderline at baseline), and HBsAg loss and HBsAg seroconversion (for subjects with HBsAg+ or borderline at baseline). Kaplan-Meier analyses of time to confirmed occurrence of each of these outcomes were also conducted.

Pharmacokinetics: Pharmacokinetic analyses were performed in subjects who provided at least one evaluable pharmacokinetic profile. Concentrations of adefovir in plasma were presented for each subject and descriptive statistics (sample size, arithmetic mean, geometric mean, standard deviation, coefficient of variation [% CV], minimum, median, and maximum) were calculated and tabulated per sampling time by treatment group. Mean and median concentration-time profiles of adefovir were plotted by treatment group. Pharmacokinetic parameters were estimated for individual subjects and summarized by treatment group using descriptive statistics. The relationship between clearance of adefovir and estimates of renal function was also evaluated.

STUDY SYNOPSIS (CONTINUED)

Statistical Methods, continued:

Safety: Safety measures were analyzed in all subjects who received at least one dose of study medication. Safety analyses by treatment group included AE presentations, maximum laboratory toxicity grades, occurrence of marked laboratory abnormalities, special analyses of hepatic and renal parameters, weight change analysis, use of concomitant medications, and time to discontinuation of study drug. Hepatic analyses comprised maximum on-treatment ALT values in ranges (multiples of ULN or of baseline value) presented with concurrent factors, and summary statistics by visit for change from baseline in serum albumin, total bilirubin, prothrombin time, and alkaline phosphatase. Renal analyses included summary statistics for change from baseline in serum creatinine and phosphorus values and calculated CL_{cr} values; resolution of treatment-emergent abnormalities of confirmed ≥ 0.5 mg/dL increases from baseline in serum creatinine and confirmed values < 1.5 mg/dL for phosphorus; minimum and final on-treatment calculated creatinine clearance values; and time to confirmed 50% reduction in calculated creatinine clearance (Kaplan-Meier method).

SUMMARY – RESULTS:

A total of 28 subjects were enrolled, 10 in the mild renal impairment group, 12 in the moderate renal impairment group, and the remainder in the severe renal impairment or ESRD with hemodialysis groups. Only two subjects with severe renal impairment were treated, and neither completed the study; one discontinued the study due to progression of hepatitis B after 19 weeks on study and the other discontinued due to the progression of renal disease after 29 weeks on study. No subjects were enrolled into Group 4A (ESRD without hemodialysis), and only four subjects were enrolled into Group 4B (ESRD with hemodialysis). The low enrollment in the renal study groups with more severe renal disease limits the extent to which the efficacy, pharmacokinetics, and safety of adefovir dipivoxil in these groups can be evaluated.

Efficacy Results:

Statistical testing demonstrated that, based on DAVG12 results, dosing with adefovir dipivoxil liquid suspension at daily dosages of 10 mg and 5 mg in the mild and moderate renal impairment study groups, respectively, was noninferior to dosing with the tablet formulation (adefovir dipivoxil 10 mg/day) in subjects with normal renal function (historical efficacy). However, it is apparent that the antiviral effect observed with the 5 mg/day dose was clearly numerically less than that observed with the 10 mg/day dose. Noninferiority was not established for protocol-specified dosing in the other two renal study groups (severe renal impairment and ESRD with hemodialysis).

STUDY SYNOPSIS (CONTINUED)

Efficacy Results, continued:

Although the sample sizes were small in the two study groups with most advanced renal disease, making the results of DAVG₁₂ noninferiority testing less robust, decreasing efficacy response was seen with decreasing dose of adefovir dipivoxil (more renal impairment) with median DAVG₁₂ in serum HBV DNA values (-2.36, -1.94, -1.06, and -0.49 log₁₀ copies/mL for the mild, moderate, and severe renal impairment groups and the ESRD with hemodialysis group, respectively). Diminishing response with decreasing dose was also reflected by median change from baseline in serum HBV DNA at the final on-treatment measurement in each group: At Week 48, serum HBV DNA concentrations had decreased by a median of 3.21 log₁₀ copies/mL in the mild renal impairment group (10 mg/day) and by a median of 2.61 log₁₀ copies/mL in the moderate renal impairment group (5 mg/day). At Week 24, the decline from baseline in serum HBV DNA concentration for the one remaining subject with severe renal impairment (2.5 mg/day) was 1.01 log₁₀ copies/mL. At Week 12, serum HBV DNA concentrations had decreased by a median of 0.94 log₁₀ copies/mL in ESRD subjects with hemodialysis (initial dose 1 mg followed by 0.5 mg after each hemodialysis session three times a week).

Three subjects with mild renal impairment and two subjects with moderate renal impairment had serum HBV DNA concentrations < 1000 copies/mL at one or more study visits. Confirmed ALT normalization was seen in 86% of those with mild renal impairment (6/7) and 89% of those with moderate renal impairment (8/9) by Week 48. Two of the subjects in the moderate renal impairment group had confirmed HBeAg loss and seroconversion. No subjects in the two most renally impaired groups met the criteria for serum HBV DNA < 1000 copies/mL, normalized ALT, or HBeAg loss or seroconversion at any time on treatment. No subject in any renal study group experienced HBsAg loss or seroconversion during the study.

STUDY SYNOPSIS (CONTINUED)

Pharmacokinetic Results: In the present study, steady-state (Week 12 and 48) adefovir plasma exposure values following administration of dose-adjusted adefovir dipivoxil liquid suspension in chronic hepatitis B subjects with mild or moderate renal impairment or with ESRD with hemodialysis were generally within the ranges observed in chronic hepatitis B subjects with normal renal function in Study GS-00-472. Steady-state median C_{max} values at Week 12 were 28.9 and 16.4 ng/mL in the subjects with mild and moderate renal impairment, respectively. At Week 12, median AUC_{tau} values were 314.3 and 275.6 ng·h/mL in the mild and moderate renal impairment groups, respectively, and the median AUC_{0-24} value was 213.2 ng·h/mL in subjects with ESRD with hemodialysis. There were insufficient pharmacokinetic data in the subjects with severe renal impairment to draw any conclusions.

Median (Min, Max)	Steady-state Pharmacokinetic Parameter Values at Week 12				Study GS-00-472 Subjects with Normal Renal Function Steady-state (Day 7)
	Renal Study Group				
	Mild (n = 9)	Moderate (n = 11)	Severe (n = 1)	ESRD w/HD (n = 3)	
C_{max} (ng/mL)	28.9 (20.1, 45.3)	16.4 (7.6, 39.4)	5.9	9.9 (7.9, 17.9)	16.7 (9.2, 38.7)
C_{tau} (ng/mL)	3.6 (1.7, 6.4)	8.8 (1.7, 20.1)	5.9	NA	2.1 (< 1.0, 10.5)
AUC (ng·h/mL)	314.3 (223.0, 524.9)	275.6 (106.7, 737.8)	110.4	213.2 (163.5, 324.9)	185.6 (124.3, 367.0)

HD = hemodialysis

AUC = AUC_{tau} for mild, moderate, and severe renal impairment groups

AUC = AUC_{0-24} for ESRD w/HD group

Safety Results: Treatment with adefovir dipivoxil oral suspension for up to 48 weeks in the four renal study groups at dosages adjusted for renal function was generally well tolerated in this study. The adverse events reported by the largest percentages of subjects were fatigue (18%); and blood creatinine increased, headache, upper abdominal pain, and nausea (14% each). Each subject in the mild, moderate, and severe renal impairment groups reported at least one adverse event while on treatment. There were no deaths in the study. Seven subjects (25%) in the safety analysis set had at least one serious adverse event (SAE) during the treatment period (one subject with mild renal impairment, five with moderate renal impairment, and one with ESRD with hemodialysis). All serious adverse events except one (hypertensive emergency) were considered to be unrelated to study treatment. Study medication was not permanently discontinued in any of the subjects as a result; however, study medication was interrupted in two of the subjects and the dosage of the study medication was reduced in one subject because of an SAE. No individual SAE was seen in more than one subject.

STUDY SYNOPSIS (CONTINUED)

Safety Results, continued:

Two subjects (7%), one with moderate and one with severe renal impairment, reported AEs that led to permanent discontinuation of study medication (increased serum creatinine and progression of renal disease, respectively).

No on-treatment Grade-4 abnormalities in serum ALT were seen in this study. Two subjects (one mild and one moderate renal impairment) had Grade-3 ALT values at Weeks 2 to 4 on study treatment (one with a concurrent Grade-4 bilirubin value). Both subjects subsequently saw substantial improvement in ALT. One subject with mild renal impairment had a Grade-3 post-treatment ALT flare.

Seven subjects overall (25%) had a confirmed increase in serum creatinine concentration of at least 0.5 mg/dL during the treatment period (four subjects with moderate renal impairment, two with severe renal impairment, and one with ESRD with hemodialysis). No subject had confirmed (two consecutive) serum phosphorus concentrations below 1.5 mg/dL while on treatment, however three subjects had Grade-2 or -3 abnormalities in serum phosphorus (1 to < 2 mg/dL) and two of these subjects had confirmed phosphorus values below 2.0 mg/dL. Two-thirds of subjects in Groups 1–4A (16 of 24 subjects) retained their screening calculated CL_{cr} category, while one subject improved by one category and seven declined by one category (minimum post-baseline value). In six subjects, the adefovir dipivoxil dosing regimen was changed per protocol as a result of decreases in calculated CL_{cr} values. These changes in renal function seem noteworthy, particularly in the moderately and severely impaired subjects. In the moderate renal impairment group, 4 of 12 subjects had declines in calculated CL_{cr} values, mandating a change to study drug regimen, and an additional subject permanently discontinued study medication due to increased serum creatinine. In the severe renal impairment group, both subjects had increases in serum creatinine, which led to a protocol-mandated reduction in drug dosage in one subject; both of these subjects permanently discontinued study medication early, one because of elevated serum creatinine/progression of renal disease and the other because of progression of hepatitis B.

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS:

Statistical testing demonstrated that dosing with adefovir dipivoxil liquid suspension at daily dosages of 10 mg and 5 mg in the mild and moderate renal impairment study groups, respectively, was noninferior to dosing with the tablet formulation (adefovir dipivoxil 10 mg/day) in subjects with normal renal function. Noninferiority with the adefovir dipivoxil 10 mg/day tablet formulation was not established for protocol-specified dosing in the two groups with most advanced renal disease (severe renal impairment and ESRD with hemodialysis). Changes in serum HBV DNA concentrations during this study suggested a decreased efficacy response with decreasing dose of adefovir dipivoxil across all renal study groups evaluated.

Steady-state (Week 12 and 48) adefovir plasma exposures in subjects with mild or moderate renal impairment and in subjects with ESRD receiving hemodialysis were generally within the ranges observed in chronic hepatitis B subjects with normal renal function who had HBV DNA responses in Study GS-00-472.

Treatment with adefovir dipivoxil oral suspension for up to 48 weeks in the four renal study groups at daily dosages adjusted for renal function was generally well tolerated in this study. However, changes in renal function as measured by serum creatinine and calculated CL_{cr} seem noteworthy, particularly in the moderate and severe renal impairment groups. It is difficult to assess what fraction of the decrease in renal function was due to the natural evolution of the preexisting nephropathy, due to adefovir dipivoxil study treatment, or due to a combination of these two factors or other unidentified factors.

The daily-dose-adjustment approach used in the current study was not clearly safer or more efficacious than the dosing-interval-adjustment approach used in some subjects in Study GS-98-435 and Study GS-01-550. Therefore the results of the current study do not support a new dosing strategy of adjustment of daily adefovir dipivoxil dose over the current strategy of adjustment of the adefovir dipivoxil dosing interval in subjects with impaired renal function.