CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-449

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA: 21-449
Submission Dates: 03/20, 05/30, 06/12, 06/13, 07/08, 07/10, and 08/29/2002
Brand Name : Hepsera™
Generic Name: Adefovir dipivoxil
Indication: Treatment of hepatitis B virus infection
Applicant: Gilead Sciences
Formulation: Tablets
Strength: 10 mg
Reviewer: Robert O. Kumi, Ph.D.
Secondary Reviewer: Arzu Selen, Ph.D., Deputy Division Director, DPE III.
Team Leader: Kellie Reynolds, Pharm.D.
OCPB Division: DPE III
OND: Division of Antiviral Drug Products

Executive Summary
Introduction and Background
Adefovir dipivoxil, (9-[2-bis[(pivaloyloxy)methyl]phosphinyl]-methoxy]ethyl]adenine or bis-POM PMEA), is an oral prodrug of adefovir (ADV), a phosphonate nucleotide analog of adenosine monophosphate. The prodrug, adefovir dipivoxil (ADV DP), is rapidly converted to ADV in plasma and during absorption from the intestine. ADV has potent activity against hepadnaviruses, retroviruses, and herpes viruses. Adefovir dipivoxil is proposed for the treatment of hepatitis B virus (HBV) infection.

Five pharmacokinetic (PK) studies and two pivotal efficacy studies were conducted in support of the ADV DP application. The clinical development program included two principal placebo-controlled phase 3 studies, GS-98-437 and GS-98-438. In these two studies patients with chronic hepatitis B infection and compensated liver disease received ADV DP 10 mg once daily. Some subjects in Study 437 received ADV DP 30 mg once daily. The sponsor provided complete 48-week efficacy data (liver histology, HBV viral load, blood chemistries and antigen status) for both studies. An exposure-response relationship was not established, but clinical evidence suggested that the 10 and 30 mg once daily adefovir dipivoxil doses were efficacious. The 30 mg once daily dose produced greater suppression in HBV viral load, but was associated with mild nephrotoxicity. Based on the advice of the safety monitoring board, only the 10 mg dose was continued for this indication. Therefore, further exploration of exposure-response relationship could not be made.

In all PK studies, adefovir dipivoxil was rapidly converted to ADV, and ADV DP was not detectable systemically 30 minutes after drug administration. ADV PK were evaluated with respect to intrinsic and extrinsic factors, including disease status (HBV, renal and hepatic impairment), drug-drug interactions and food. Generally, extrinsic factors did not alter adefovir PK. The degree of renal impairment (renal function) was the only identified intrinsic factor that significantly affected ADV exposure. This finding is expected because adefovir is eliminated renally; thus, subjects with impaired renal function with creatinine clearance less than 50 mL/min will require dose adjustments. Following an IV dose, the mean total clearance of adefovir was 223 mL/hr/kg and the approximated mean renal clearance was 205 mL/hr/kg

Recommendations
The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to the Human Pharmacokinetics and Biopharmaceutics Section of NDA 21-449. In general, the information, presented is acceptable and supports approval of the proposed adefovir dipivoxil 10 mg once daily dose. Based on the review of the clinical pharmacology and biopharmaceutics information, the following

recommendations can be made regarding adefovir dipivoxil dosing with regard to meals, drug-drug interactions, and patients with hepatic or impaired renal function.

- The dose of adefovir dipivoxil in chronic hepatitis B patients with creatinine clearance greater than or equal to 50 mL/min is 10 mg once daily
- Adefovir dipivoxil 10 mg can be administered without regard to meals
- Adefovir dipivoxil 10 mg can be coadministered with acetaminophen, lamivudine, or sulfamethoxazole/trimethoprim. Adequate safety precautions should be undertaken when adefovir dipivoxil is coadministered with nephrotoxic agents, such as ibuprofen (non-steroidal agents and immunosuppressants) and other agents that alter renal function, particularly agents that undergo active tubular secretion (anionic transporter).
- Subjects with severely or moderately impaired hepatic function (Child Pugh classification system) with adequate renal function (CL_{cr} equal to or greater than 50 mL/min) do not require a dose adjustment.
- Subjects with impaired renal function with creatinine clearance less than 50 mL/min require dosage adjustments, and adefovir dipivoxil should not be given in non-hemodialysis subjects with creatinine clearance less than 10 mL/min.

Phase IV Commitments

Conduct study 526 to determine safety, efficacy and optimal dosing (based on creatinine clearance) in renally impaired patients with chronic hepatitis B. Include complete pharmacokinetic assessments (plasma concentration-time profiles) at treatment initiation (Day 0) and following chronic dosing.

Characterize the specific renal transport pathways of adefovir in vivo (anionic vs. cationic transport). Once determined, evaluate the potential for drug interactions between adefovir and drugs that are renally eliminated and may be co-administered in patients with coexisting diseases.

Provide additional pharmacokinetic data in non-Caucasian subjects and further evaluate the efficacy and safety of adefovir dipivoxil in ethnic groups that were underrepresented in the pivotal trials.

Conduct drug interaction studies of adefovir dipivoxil with cyclosporine, tacrolimus, pegylated interferon, tenofovir disoproxil fumarate and didanosine.

/S/

_____ Date_____

Robert O. Kumi, Ph. D.
Clinical Pharmacology Reviewer

/S/

_____

Arzu Selen, Ph. D.
Acting Clinical Pharmacology Team Leader

Table of Contents

Summary of Clinical Pharmacology and Biopharmaceutics Findings

Clinical Pharmacology and Biopharmaceutics Program for Adefovir Dipivoxil

A dose of 10 mg ADV DP is proposed for the treatment of HBV infection. Studies reviewed in detail are listed below:

1) Study 476: Food Effect (n =18), 10 mg single dose; healthy volunteers
2) Study 474: Hepatic Impairment (n = 24), 10 mg single dose. Three groups (n = 8, per group): Normal, Child Pugh Class B and Child Pugh Class C according to hepatic function
3) Study 473: Renal Impairment (n = 41), 10 mg single dose. Five groups (n ≈ 8, per group), normal, mild, moderate and severe with respect to renal function, and end stage renal disease requiring dialysis
4) Study 475: Drug-drug interaction (n = 71), 10 mg single dose with/without coadministered drug (lamivudine, ibuprofen, acetaminophen, sulfamethoxazole/trimethoprim) at specified dose
5) Study 472: Pharmacokinetics in target population (n = 14), 10 mg single and multiple dose in patients with Hepatitis B Virus Infection
6) Gentest Study Report: *In vitro* metabolism; determination of inhibitory potential of adefovir and adefovir dipivoxil
7) Dissolution method development
8) PGP Study in knock out and wild type mice

Additional studies provided in this submission were obtained from a previous NDA submission for an HIV indication. The Office of Clinical Pharmacology and Biopharmaceutics previously reviewed the studies submitted to . The studies submitted in were not reviewed again; however, relevant findings from the HIV program are included in this review.

This section of the review summarizes the key clinical pharmacology and biopharmaceutics findings related to adefovir dipivoxil 10 mg for the treatment of HBV infection:

Key Clinical Pharmacology Findings (NDA 21-449,)

Absorption: Approximately 60 % of adefovir is absorbed following administration of adefovir dipivoxil. ADV DP was not available systemically. Food delays the median ADV T_{max} by approximately 2 hours, but does not have an appreciable effect on ADV AUC and C_{max}; therefore, ADV DP can be administered without regard to meals.

- Maximal adefovir concentrations were obtained within 5 hours (median T_{max} < 3 hours), followed by a biexponential decline in drug concentrations. The mean terminal half-life was ≈ 7 hours.

- Pharmacokinetics of adefovir were dose-independent following single and multiple dose administration over the range 10 mg to 250 mg adefovir dipivoxil once daily dose. Single dose PK are predictive of multiple dose PK and no drug accumulation is present upon multiple dosing.

- Distribution: Adefovir binding to plasma and serum proteins is low (4 %). The mean volume of distribution was ≈ 370 mL/kg following an intravenous dose of 1 or 3 mg/kg/day.

- Pharmacokinetic results from all PK studies, except the hepatic impairment study (moderate and severe groups, CV > 40 %) were characterized by low variability (CV < 30 %). The probable sources of variability in the hepatic impairment study were likely the small number of patients and the effect of hepatic disease.

- General pharmacokinetic characteristics of adefovir did not differ significantly because of demographic factors, disease status (HBV-infected/HIV-infected/healthy volunteers) and gender. Insufficient data were provided to assess the effect of race and age on adefovir PK.

- Although adefovir exposure in patients with moderate and severe hepatic impairment was comparable to adefovir exposure in subjects without hepatic impairment following a single dose administration of ADV DP 10 mg; the half-life in subjects with impaired hepatic function is longer than in subjects with normal hepatic function.

- The degree of renal impairment affected adefovir exposure; subjects with creatinine clearance < 50 mL/min will require dosage adjustment using the following schedule:

Adefovir dipivoxil dosage in renal impairment

Calculated Creatinine Clearance (mL/min)	10 mg Dose in given Interval
≥ 50	Once every 24 hours
20 – 49	Once every 48 hours
10 – 19	Once every 72 hours
ESRD requiring hemodialysis*	Once weekly following hemodialysis

*hemodialysis removed 35 % of ADV from the systemic circulation

- Metabolism/Elimination: Clearance of adefovir is attributed to renal secretion. Approximately 90 % of intravenously administered ADV is recovered unchanged in the urine, and up to 12 hours after administration, no metabolites of ADV were detected in the urine or in serum samples. Following intravenous administration, the median ADV renal clearance exceeds the glomerular filtration rate, indicating net active tubular secretion in addition to glomerular filtration; however, the exact renal elimination mechanism (relative contribution of each pathway) has not been identified. Following single or multiple dose administration of ADV DP, approximately 40 % of the administered oral dose is recovered as adefovir in the urine over a twenty-four period.

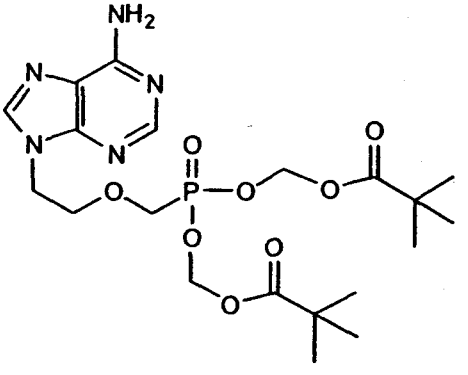
- Drug-drug interactions: Based on *in vitro* metabolism data, both adefovir and ADV DP have a low potential to undergo metabolically-based drug-drug interactions. However, since ADV is eliminated renally, it may interact with drugs eliminated renally by a similar mechanism or alter renal function. ADV's induction potential on CYP enzymes and the role of drug transporters such as PGP on ADV PK are unknown.

Question-Based Review

1. What are the general attributes of adefovir dipivoxil and adefovir dipivoxil formulations?

1.1 Physico-chemical characteristics

The chemical name of adefovir dipivoxil (ADV DP) is 9-[2 [[bis[(pivaloyloxy)-methoxy] phosphinyl] methoxy] ethyl]adenine. It has the following structural formula:



Characteristics of ADV DP

molecular formula: $C_{20}H_{32}N_5O_8P$	molecular weight of 501.48 g.
white to off-white crystalline powder	intrinsic aqueous solubility of 0.34 mg/mL
octanol/aqueous phosphate buffer (pH 7) partition coefficient (*log p*) of 1.91	inactive ingredients: pregelatinized starch (gluten free), croscarmellose sodium, lactose monohydrate, talc, and magnesium stearate.

The tradename of adefovir dipivoxil is Hepsera™. The proposed ADV DP dose in chronic hepatitis B infection with CL_{cr} equal to or greater than 50 mL/min is 10 mg once daily.

1.2 Proposed mechanism of drug action and therapeutic indication

Adefovir is a synthetic nucleotide analog of adenosine 5'-monophosphate. *In vivo*, adefovir dipivoxil is converted to the parent compound, adefovir, and through two phosphorylation reactions to adefovir diphosphate. Adefovir diphosphate exhibits activity against the hepatitis B virus (HBV) DNA polymerase. ADV DP is proposed for the treatment of CHB infection.

1.3 Efficacy and safety information that contribute to the assessment of clinical pharmacology and biopharmaceutics study data.

Efficacy and safety information obtained in the two pivotal efficacy trials, GS-98-437 (n = 511) and GS 98-438 (n = 184) suggest that the adefovir dipivoxil 10 mg once daily dose is safe and effective (See Medical Officer's Review). In [redacted], when higher ADV DP doses were studied (adefovir dipivoxil dose ≥ 60 mg once daily), nephrotoxicity was the most apparent adverse event associated with adefovir treatment. Additionally, long term therapy with adefovir dipivoxil 60 mg once daily led to a decrease in ADV apparent oral clearance (week 52 CL/F was 269 ± 90 mL/hr/kg vs. week 2 CL/F was 414 ± 106 mL/hr/kg) leading to increased ADV exposure.

In the pivotal trials and other supporting studies for the proposed indication, chronic hepatitis B (CHB) infection, subjects with CHB infection received 10 mg or 30 mg ADV-DP once daily or placebo. Pharmacokinetic data were not obtained in either of these trials; however, the 30 mg once daily dosing was discontinued due to the occurrence of mild reversible nephrotoxicity. According to the Medical

Reviewer, nephrotoxicity was rarely observed at the 10 mg once daily dose in patients with normal renal function.

In the previous trials, adefovir dipivoxil doses ≥ 60 mg once daily were associated with depletion of L-carnitine stores; thus, supplemental L-carnitine (500 mg) was administered with ADV DP in clinical trials. However, at the 10 mg dose level, serum carnitine levels are not depleted and L-carnitine administration is not required.

2. What are the general clinical pharmacology characteristics of adefovir?

2.1 Selection and Measurement of Surrogate endpoints

The primary surrogate endpoint for chronic hepatitis B (CHB) infection is liver histology. HBV infection occurs when viral DNA is incorporated into the genome of hepatocytes, which stimulates a host immune response leading to inflammation. As indicated previously (Mechanism of Action, Section 1.2), adefovir, via adefovir diphosphate, exhibits activity against the hepatitis B virus (HBV) DNA polymerase. In the absence of drug intervention, the liver may undergo histological changes if the immune response of the host is insufficient to raise antibodies and clear the infection. Therefore, liver histology determined by taking liver biopsies at baseline and week 48 provide a reasonable basis of comparison to evaluate a drug's therapeutic effect.

Liver biopsies are evaluated for necrosis, inflammation, and fibrosis to assess the extent and severity of liver damage according to a grading system. In this development program, the Knodell Histologic Activity Index (HAI) grading system was used. The HAI system has four components: periportal ± bridging necrosis (0 – 10 scale), interlobular degeneration and focal necrosis (0 – 4 scale), portal inflammation (0 – 4 scale) and fibrosis (0 – 4 scale). Other surrogate markers for CHB infection use seroconversion (loss of antigen and appearance of antibodies), serum HBV DNA viral load (Roche Amplicor assay), and ALT measurements.

2.2 Determination of PK measures for assessment of exposure-response relationships

Adefovir was adequately measured in the plasma; therefore, one could estimate relevant ADV PK measures and parameters, such as AUC, C_{max}, and apparent oral clearance (CL/F). ADV serves as a surrogate for the active moiety because adefovir diphosphate can not be measured accurately in the blood. Refer to section 6 of the QBR for further details on how adefovir concentrations were determined.

2.3 Adefovir exposure-response relationships

Exposure-response relationships have not been established between ADV or ADV diphosphate exposure and efficacy. Based on empirical information, the 30 mg dose produces mildly reversible nephrotoxicity whereas the 10 mg rarely produced nephrotoxicity in subjects with adequate renal function. Doses between 10 and 30 mg have not been studied. The sponsor used a hyperbolic function to estimate (simulate) efficacy of the 10 mg dose. The only details of this modeling approach were provided in the application summary. Based on the sponsor's modeling, the efficacy of the 10 mg dose would be greater than the efficacy at the 5 mg dose, and approach the efficacy of the 30 and 60 mg dose. The sponsor's modeling showed that the 20 mg dose would be more effective than the 10 mg dose; however, the sponsor dose not indicate why the 10 mg dose was selected instead of the 20 mg dose or any dose less than 30 mg.

2.4 Dose and time dependency of adefovir pharmacokinetics:

The pharmacokinetics of ADV were dose-independent following administration over the range of 10 to 250 mg after single- and multiple-dose administration. In the CHB program, only the 10 mg dose was evaluated, however these data can be bridged to existing data —— to extend the dose-

proportionality range. There was some indication that the C_{max} increased in a less than dose-proportional manner at the 500 mg dose.

Mean (SD) ADV PK Measures for 10 mg (NDA 21-449)

Daily Dose (mg)	10 (n = 11)*		60 (n = 6)		125 (n = 9)		250 (n = 9)		500 (n = 9)	
Day	1	7	1	14	1	14	1	14	1	14
AUC (μg hr/mL)	0.23 (0.07)	0.22 (0.08)	1.10 (0.16)	1.15 (0.23)	ND	ND	3.76 (1.28)	3.22 (0.85)	6.65 (1.44)	6.15 (1.31)
C_{max} (μg/mL)	0.019 (0.006)	0.020 (0.008)	0.10 (0.02)	0.11 (0.02)	0.21 (0.13)	0.24 (0.08)	0.44 (0.07)	0.45 (1.14)	0.83 (0.14)	0.64 (1.13)
CL/F mL/hr/kg	421 (118)	471 (154)	422 (82)	414 (106)	ND	ND	592 (169)	666 (112)	578 (98)	631 (102)

* On day 7, n = 14

The pharmacokinetics of adefovir were comparable on Day 1 and 7 in the target patient population. The PK of ADV following long-term dosing of adefovir dipivoxil 10 mg once daily have not been determined. In a previous study (, following ADV-DP 60 mg once daily administration, the CL/F of ADV at Week-52 was 35 % lower than at Week-2. The change in CL/F was attributed to nephrotoxicity. Generally, a change in CL/F is not anticipated at the 10 mg dose level; however, it is advisable to confirm that CL/F remains constant during long-term CHB treatment.

2.5 Comparison of adefovir pharmacokinetics: CHB infected patients vs. healthy subjects
Generally, the PK of ADV in CHB infected subjects are comparable to those in healthy subjects as shown in Table. below

ADV PK Comparisons: HBV infected Subjects vs. Healthy Subjects* (10 mg single dose of ADV DP)

C_{max} (ng/mL)	N = 11 (HBV infected subjects)	N = 8 (Healthy Subjects)
Mean ± SD	19.49 ± 6.14	18.80 ± 4.80
Range		
T_{max} (hr)		
Median	1.00	1.25
Range		
$AUC_{0-\infty}$ (ng•hr/mL)		
Mean ± SD	233 ± 66	202 ± 46
Range		
$T_{½\lambda z}$ (hr)		
Mean ± SD	7.5 ± 1.7	6.3 ± 0.6
Range		
CL/F (mL/min)		
Mean ± SD	421 ± 118	468 ± 92
Range		

* Data from hepatic impairment study (subjects with normal hepatic function)

Information from the previous submission (Study GS-99-430) indicates that HIV-infected subjects have comparable PK to healthy subjects. In sum, HIV-infected subjects and CHB-infected subjects have comparable ADV PK to healthy subjects. The interpatient variability was low (< 30 %) in both CHB infected patients and healthy non-CHB subjects.

2.6 Metabolism and Excretion: Elimination route
Adefovir is eliminated renally with limited or no metabolism. In previously conducted studies GS-92-201, -202 and –203 (Re: Dr. Sekar's review) following administration of intravenous adefovir dose, 90 % of the dose was eliminated in the urine as unchanged parent compound. Additionally, 12 hours post dose, no

metabolites of adefovir were detected in the urine or serum. ADV CL was attributed entirely to renal clearance based on a comparison of total serum clearance (223 ± 53 mL/hr/kg, n = 28) of the drug to approximated renal clearance (205 ± 78 mL/hr/kg, n = 25) following the IV dose. The baseline creatinine clearance, which serves as a measure of glomerular filtration rate, in these subjects was 88 ± 18 mL/hr/kg. Hence, the clearance of adefovir that exceeds the GFR is attributed to net active tubular secretion of the drug. The potential contribution of reabsorption is not known.

2.7 Dose and Dosing Regimen in Patients with CHB infection

The dose and dosing regimen proposed by the sponsor are consistent with the available PK data and results obtained in the efficacy trial. However, the proposed regimen has been evaluated for safety and efficacy primarily in patients with CHB without coexisting conditions. Studies are ongoing in other populations (liver transplant, HIV coinfected subjects) that are likely to require adefovir therapy. Based on available drug-drug interaction information and information in different patient populations, it is unlikely that dose-modifications will be required in these populations. Dosage recommendations for other special populations are described in a later section of the review.

3. Which intrinsic factors (renal and hepatic function, age, race, weight) affect adefovir exposure?

The only evaluable intrinsic factor that affects adefovir exposure and requires dose modification is renal function (degree of renal impairment). Gender did not affect ADV exposure. The effects of race or age on ADV exposure could not be assessed because insufficient data were provided. The sponsor provided data in the table below to summarize ADV steady-state exposure stratified by selected demographic factors.

Demographic Variable	N	Mean ± SD AUC (ng·hr/mL)	Mean ± SD C_{max} (ng/mL)
Males	47	202 ± 50	20.9 ± 6.1
Females	41	222 ± 46	23.0 ± 4.8
Caucasian	65	211 ± 47	22.5 ± 5.8
Black	15	201 ± 49	18.7 ± 4.9
Asian	6	241 ± 63	23.2 ± 5.3

3.1 Hepatic Impairment

Impaired hepatic function, determined by Child Pugh score, did not significantly affect ADV PK. This conclusion is based on a comparison of ADV exposure after a 10 mg ADV DP single dose in subjects with impaired hepatic function to exposure in subjects with normal hepatic function (Table I).

Table I: Effect of Hepatic Impairment on Adefovir Exposure

	Moderate*/Healthy		Severe/Healthy	
	GMR (%)	90 % CI	GMR (%)	90 % CI
$AUC_{0-\infty}$	126.28	79.73 - 200.01	107.77	78.96 - 147.10
C_{max}	86.44	58.34 - 128.08	78.46	61.85 - 99.52

GMR – geometric mean ratio; Moderate- Child Pugh Class B and Severe- Child Pugh Class C

*The geometric mean AUC was significantly affected by two subjects with impaired renal function: all subjects (n = 6)- 219 and excluding subjects (n = 4)- 148. GMR = 80 % if two subjects are excluded and CI will be narrower.

The upper boundary of the 90 % confidence interval (CI) associated with the geometric mean ratios was greater than 100 % in all cases, except for the C_{max} in the severe hepatic impairment group. The wide variability noted in the CIs is mainly due to the interpatient variability in subjects with impaired hepatic function (Table II). The source(s) of variability was not identified, but was likely due to the limited number of subjects, particularly in Group B where data from two subjects with renal impairment (Cl_{Cr} < 50 mL/min) were included in the comparisons.

Table II: Summary of ADV Pharmacokinetic Parameters Following 10 mg Dose

	AUC_{0-t} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{½\lambda z}$ (hr)
Normal Hepatic Function (N = 8)					
Gmean (95 % CI)	185 (154 – 223)	198 (166 – 236)	18 (15 – 23)	NA	NA
Range					
Moderate Hepatic Impairment, Child Pugh Class B (N[a] = 6)					
Gmean (95 % CI)	219 (104 – 459)	250 (130 – 481)	16 (9 – 27)	NA	NA
Range					
Severe Hepatic Impairment, Child Pugh Class C (N = 8)					
Gmean (95 % CI)	190 (123 – 293)	213 (145 – 314)	14 (11 – 18)	NA	NA
Range					

Gmean – geometric mean; CI – confidence interval

NA = Not applicable; [a]Subjects 0592-1003 and 0592-1009 had extrapolated % $AUC_{0-\infty}$ greater than 30 % and therefore, in accordance with the protocol, were not included in the summary statistics.

Two significant observations from the hepatic impairment study were that 1) half-life increased with impaired hepatic function and 2) subjects who have both impaired renal function and impaired hepatic function are likely to have increased exposures relative to subjects with the same degree of hepatic impairment and normal renal function. The second finding was expected because adefovir is cleared renally and ADV exposure increases with diminishing renal function. The first finding of increased half-life with impaired hepatic function was not anticipated because ADV is not cleared by hepatic processes. Consequently, there is no clear mechanistic basis for the half-life observation. There did not appear to be a relationship between half-life (elimination rate constant, k) or volume of distribution (V) and apparent oral clearance. It is possible that other intrinsic patient factors could impact the half-life of adefovir in patients with impaired hepatic function; however, these potential factors can not be determined from the provided information.

Comment

During the Clinical Pharmacology Briefing for this NDA, the apparent increase in half-life was discussed at length. The main conclusion from the briefing discussion was that additional PK studies in this patient population were not needed, because 1) there was no mechanistic basis for the increased half-life 2) drug accumulation, due to increased half-life, would not be significant (< 1.5-fold). Although this conclusion is reasonable, this Reviewer thinks that it is important to determine the potential impact of increased half-life on safety in a multiple-dose context, particularly in subjects with renal and hepatic impairment. It is possible that drug disposition in such subjects may differ from subjects with only impaired hepatic or renal function, respectively. Such subjects are likely to have an increased incidence of adefovir-related adverse events, if drug exposures increase, due to accumulation, in an unexpected manner. The sponsor has indicated that they will conduct a multiple-dose study in patients with chronic hepatitis B and impaired renal function. Since most subjects with chromic hepatitis B may have varying degrees of hepatic dysfunction, results form this study may address this reviewer's concerns about potential increases in adefovir exposure in patients with impaired hepatic function.

3.2 Renal Impairment

Following administration of a single 10 mg dose of ADV DP subjects with increasing degrees of renal impairment had increased ADV exposure (Table III). This finding was expected because ADV is eliminated renally, and CL_R decreases with increasing severity of renal impairment.

Table III: Single Dose Adefovir Pharmacokinetic Parameters in Subjects with Varying Degrees of Renal Function

	Renal Function			
	Normal (N = 7[a])	Mild Impairment (N = 8)	Moderate Impairment (N = 7)	Severe Impairment (N = 10)
C_{max} (ng/mL)				
Mean ± SD	18 ± 3	22 ± 4	28 ± 9	52 ± 10
Range				
$AUC_{0-\infty}$ (ng•hr/mL)				
Mean ± SD	201 ± 41	266 ± 56	455 ± 176	1244 ± 629
Range				
CL/F (mL/min)				
Mean ± SD	469 ± 99	356 ± 86	237 ± 118	92 ± 51
Range				
CL_{Cr} (mL/min)				
Mean ± SD	109 ± 25	66 ± 16	40 ± 9	18 ± 6

a The extrapolated % $AUC_{0-\infty}$ for subject 1085-0001 was greater than 30 %; therefore, in accordance with the protocol, data from this subject were not included in the summary statistics.

The data in Table III indicate that dosage adjustments will be required for subjects with $CL_{cr} < 50$ mL/min. It is noted that the median concentrations at 96 hours post dose were approximately 1.5 ng/mL ( ) in all groups.

Hemodialysis removed 35 % of the adefovir dose from the plasma. The estimated median $CL_{dialysis}$ was 133.79 mL/min.

3.2.1 Proposed Dosing in Renal Impairment

The adefovir dipivoxil dosing recommendations for subjects with normal and impaired renal function and subjects requiring hemodialysis are summarized in Table IV.

Table IV: Proposed Adefovir dipivoxil dosage

Calculated Creatinine Clearance (mL/min)	10 mg in given Dosing Interval	Reviewers recommendation
≥ 50	Once every 24 hours	Acceptable
20 – 49	Once every 48 hours	Acceptable
10 – 19	Once every 72 hours	Acceptable
< 10	Once weekly	Unacceptable
ESRD requiring hemodialysis	Once weekly following hemodialysis	Acceptable

In general, the sponsor's dosing proposals are acceptable because they are supported by the exposure data. Data were not provided for non-hemodialysis subjects with $CL_{cr} < 10$ mL/min, yet the sponsor has provided a dosing recommendation for these patients. After extensive discussion, the sponsor and FDA agreed that the label would not have dosing recommendations for non-hemodialysis patients with CL_{Cr} less than 10 mL/min.

3.22 Derivation of Dosing Algorithm

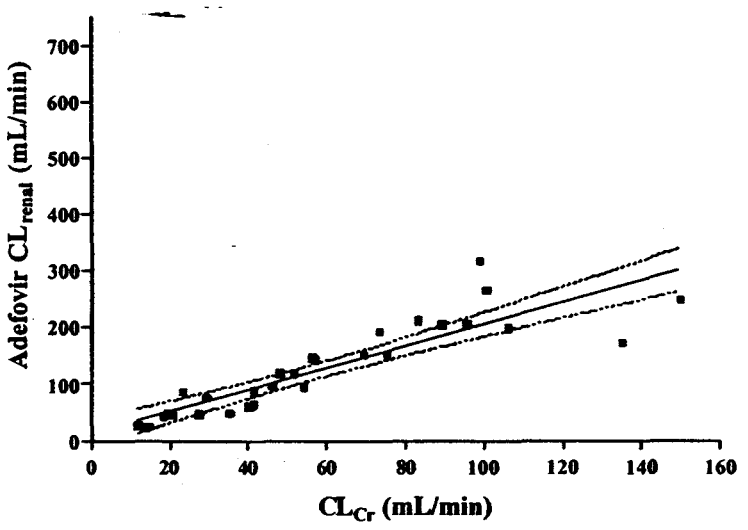
The sponsor adopted the recommendations of the *Guidance for Industry* regarding renal impairment.

1a . Conducted a linear regression analysis to show the relationship between CL_{Cr} and CL_{renal}

The relationship between CL_{renal} and CL_{Cr} was linear over the CL_{Cr} range of This finding indicates that changes in adefovir renal excretion are predicted by the degree of renal function impairment based on CL_{Cr}. It is noted that ADV CL_{renal} was approximately twice the calculated CL_{Cr}

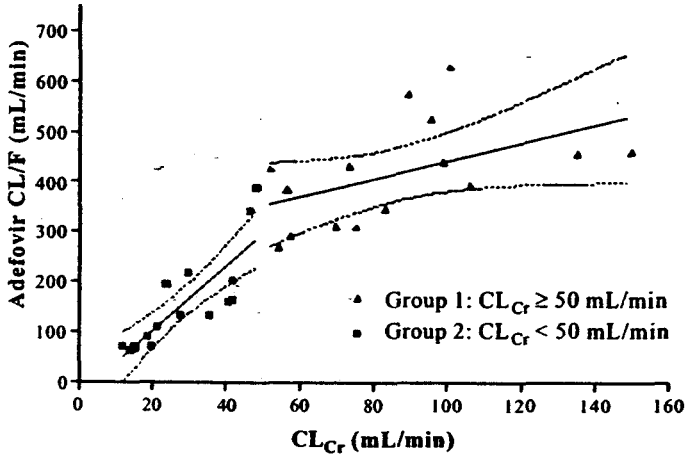
(based on slope 1.93) in all stages of renal dysfunction, suggesting that net tubular secretion of ADV is preserved despite progressive renal damage.

Figure: Relationship between CL_{cr} and CL_{renal}



1b Established a relationship between CL_{Cr} and ADV CL/F and exposure (C_{max} and AUC).
The relationship between CL/F and CL_{Cr} was characterized by two lines, with two different slopes. These two lines correspond to subjects with CL_{Cr} 50 mL/min (normal to mild renal impairment) and CL_{Cr} < 50 mL/min (moderate to severe renal impairment). The slope of the line in subjects with CL_{Cr} < 50 mL/min was approximately 4-times steeper than the slope for subjects with CL_{Cr} > 50 mL/min. The differences in the slopes for the two groups suggest that the two groups exhibit different ADV PK. It is noted that systemic adefovir exposure measures ($AUC_{0-\infty}$, C_{max}) versus CL_{Cr} yielded two different slopes, corresponding to the CL_{Cr} groups previously described.

Figure : Relationship Between Adefovir Apparent Clearance (CL/F) and Calculated CL_{Cr} (mL/min) (Linear Regression With 95 % Confidence Band)



2. Carried out simulations to determine the adefovir exposures that will be obtained at the proposed dosing frequencies for the various renal impairment groups.

Simulated Adefovir Steady State Pharmacokinetics Following Dose Interval Adjustment

	Renal Impairment			
	CL_{Cr} = 20 to 49 mL/min (every 48 hours)		CL_{Cr} = 10 to 19 mL/min (every 72 hours)	
	Simulated	**% Ratio[a]**	**Simulated**	**% Ratio[b]**
$AUC_{0-\tau}$ (ng•hr/mL)	537	113 %	1332	187 %
C_{max} (ng/mL)	33.5	161 %	53.2	255 %
C_{trough} (ng/mL)	1.42	52 %	2.37	87 %

a Ratio of simulated parameters obtained over a 48-hour dosing interval in subjects with CL_{Cr} 20 to 49 mL/min to the simulated parameters obtained over two 24-hour dosing intervals (48 hours) in subjects with $CL_{Cr} \geq 50$ mL/min

b Ratio of simulated parameters obtained over a 72-hour dosing interval in subjects with CL_{Cr} 10 to 19 mL/min to the simulated parameters obtained over three 24-hour dosing intervals (72 hours) in subjects with $CL_{Cr} \geq 50$ mL/min. Median (min, max) predicted values from compartmental analysis.

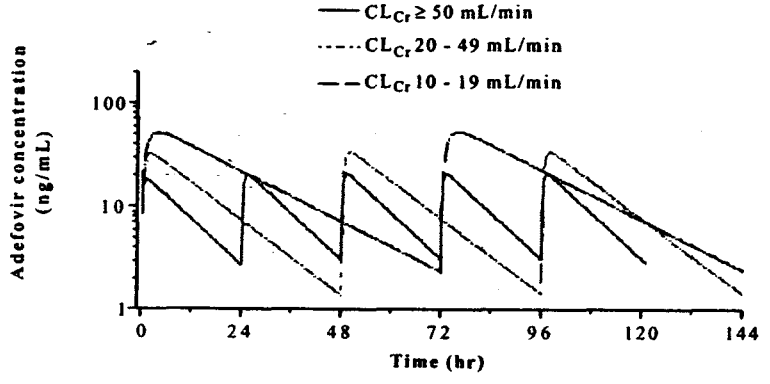
Non-Hemodialysis Patients

The simulations conducted by the sponsor are acceptable in this Reviewer's opinion, although the simulations have some limitations. The simulations were based on a linear one-compartment model, with first order input and first order elimination. The proposed model adequately described the mean and median PK data for subjects with severe and moderate renal impairment. Inspection of individual data (plasma concentration-time profiles) suggested that the one-compartment linear model suitably depicted the adefovir PK of most subjects. However, a linear pharmacokinetic model (first order input and first order output) could not adequately describe the pharmacokinetics of some subjects. The source of the apparent non-linearity could not be determined in this study; however, this apparent non-linearity should be explored in an appropriately designed pharmacokinetic study.

Despite the apparent limitations of the model and ensuing simulations, the proposed dosing recommendations are reasonable, because of the following:

1. Based on the single-dose PK information, the proposed dose adjustments will provide adequate adefovir exposure and limit drug accumulation in subjects with CL_{cr} between 10 and 50 mL/min.
2. Only one dosage strength is available, therefore, dose-adjustments can only be made by altering the dosing interval and not the dose. Considering this limitation, the proposed dosing adjustments are satisfactory for non-hemodialysis subjects with CL_{cr} between 10 and 50 mL/min.

Simulated Adefovir Steady State Concentration-Time Profiles (Dose Interval Adjusted)



The results of the simulations suggest that subjects with moderate and severe renal impairment will achieve higher C_{max} and AUC, and lower C_{min} than subjects with CL_{cr} > 50 mL/min. The clinical impact of these differences in exposure is unclear. However, the suitability of these simulations will be evaluated in a future study.

Hemodialysis Patients

The sponsor's proposed once weekly dosing of ADV DP in hemodialysis patients is reasonable. Following administration of a single 10 mg dose of ADV DP, thirty-five (35 %) percent of the absorbed adefovir dose, was removed by hemodialysis. However, shortly after dialysis was complete, the plasma concentration-time profile was flat suggesting that there was no extrarenal component for adefovir removal. Thus, it can be concluded that only dialysis removes the study drug from the plasma in these subjects. As indicated previously, 35 % of the adefovir dose was removed from the plasma following a single dialysis session, thus a significant portion of the adefovir dose should be removed after three dialysis sessions. Most patients on dialysis receive two-to-three dialysis sessions, thus the sponsor's proposal for once weekly dosing in hemodialysis patients is reasonable. It is noted that the sponsor did not provide simulated data for patients on dialysis.

4 Which Extrinsic factors affect adefovir pharmacokinetics?

Two of the most relevant extrinsic factors that may affect ADV PK are drug-drug interactions and food.

4.1 Food Effect

Food did not appear to have a significant effect on ADV exposure, as shown in Table I. Consequently, adefovir dipivoxil can be administered without regard for meals.

Table I: Summary of relative ADV Pharmacokinetic Parameters in Fasted and Fed States following single 10 mg dose of adefovir DP

	% GMR (Fed/fasted)	Ninety % CI for GMR
C_{max} (ng/mL)	87.4	79.7 – 95.8
AUC_{0-t} (ng•hr/mL)	98.8	87.3 – 111.7
T_{max} (hr) Median Range	0.76	3.00

GMR – geometric mean ratio; CI- confidence interval

4.2 Drug-Drug Interactions

Based on *in vitro* metabolism data and *in vivo* drug-drug interaction information, ADV has a low potential to undergo metabolic drug-drug interactions. However, because adefovir is eliminated renally by active tubular secretion, ADV may interact with drugs that are also eliminated renally.

4.2.1 *In vitro* metabolism (Inhibition Studies)

Neither ADV nor ADV-DP appears to be potent inhibitors or substrates of CYP enzymes. *In vitro* studies were carried out to determine the inhibition potential of ADV and ADV-DP using model substrates for common CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). ADV did not inhibit any of the listed CYP enzymes. On the other hand, at high concentrations ADV DP inhibited CYP3A4 with a mean apparent K_i that was substrate dependent (K_i was 9 μM for midazolam-1'-hydrolase activity and K_i was 45 μM for testosterone-6β-hydroxylase activity). It should be noted that ADV-DP is not

detected systemically following administration of ADV DP, thus the findings from this *in vitro* metabolism study are not likely to influence ADV DP drug interactions *in vivo*. In [redacted] *in vitro* metabolism studies were also conducted to characterize ADV's CYP inhibitory potential and substrate status. The findings reported in [redacted] were in agreement with the studies submitted in this NDA.

4.2.2 Interaction with transporters and induction potential

ADV's potential to interact with other enzyme systems or drug transporters has not been adequately characterized. The sponsor provided data from an animal study that evaluated ADV pharmacokinetics in mice without the PGP transporter (MDR1a-/-deficient or knockout mice) and wild-type mice. The use of multiple animals to generate plasma concentration-time profiles appeared to introduce a high degree of variability in the pharmacokinetic data, which complicated data interpretation. Additionally, only a limited number of collected and evaluable data points were available for the estimation of C_{max}. Consequently exposure comparisons are likely to be flawed and study findings are inconclusive. Furthermore, it is not clear if the results from animal studies are applicable to humans. The sponsor will be advised to conduct an appropriate study in humans to evaluate the role of transporters, such as PGP, on ADV PK.

The sponsor has not evaluated the induction potential of adefovir on CYP enzymes following administration of ADV-DP. This is evaluation is important because drugs coadministered with ADV DP may be CYP substrates.

4.2.3 *In vivo* drug-drug interaction studies

ADV presence did not affect the exposure of ibuprofen, lamivudine, sulfamethoxazole/trimethoprim, acetaminophen, and ibuprofen, and ADV exposure was not affected significantly by any of the listed drugs apart from ibuprofen. Results from the drug-drug interactions are summarized in the Table below.

Relative ADV Exposure Measures in ADV drug-drug interaction studies

	C_{max} (ng/mL)	AUC_{0-T} (ng·hr/mL)
	GMR (90 % CI)	GMR (90 % CI)
ADV alone	99.7 (91.4 – 108.8)	99.2 (92.5 – 106.5)
ADV + Lamivudine (100 mg)		
ADV alone	132.6 (120.6 – 145.7)	122.7 (112.9 – 133.4)
ADV + Ibuprofen (800 mg)		
ADV alone	111.5 (103.1 – 120.6)	107.6 (103.5 – 111.9)
ADV + Acetaminophen (1000 mg)		
ADV alone	97.5 (89.4 – 106.4)	109.3 (103.2 – 115.8)
ADV + Trimethoprim (160 mg)/ sulfamethoxazole (800 mg)		

ADV-DP dose 10 mg

Generally, geometric mean ratios were approximately 100 % and the associated 90 % confidence intervals were within 80 to 125 % (data not shown for coadministered drugs). Consequently, no adefovir dose adjustment is required for coadministration of adefovir with any of these agents. In the adefovir-ibuprofen study, adefovir exposure increased by approximately 30 %; whereas adefovir exposures were not affected by any of the other coadministered drugs. The clinical impact of the increased adefovir exposure upon coadministration with ibuprofen is unknown. The mechanism of the ibuprofen-adefovir interaction was unclear, but may be due to increased ADV bioavailability, because renal clearance remained unchanged.

Because, adefovir and ibuprofen are nephrotoxic, coadministration of these two compounds may result in drug-drug interaction (pharmacodynamic/pharmacokinetic) that my have clinical impact. Consequently, coadministration of ADV DP with ibuprofen, and with any other nephrotoxic agents should be undertaken with caution.

4.2.3.1 Rationale for drugs selected

The agents studied in this clinical trial represent agents that are likely to be used by a substantial portion of the chronic HBV-infected population. Lamivudine may be used in combination with ADV for HIV/HBV co-infected patients or in combination therapy for HBV infection. Ibuprofen and acetaminophen were used frequently (based on query) in controlled clinical trials of ADV DP for chronic HBV infection. In addition, renal toxicity is associated with ibuprofen use and acetaminophen exhibits hepatotoxicity. These two toxicities are of concern with adefovir because ADV DP is associated with renal toxicity and is used to treat hepatic conditions. Essentially, pharmacodynamic as well as PK interactions may occur when either ibuprofen or acetaminophen are coadministered. Finally, Trimethoprim/sulfamethoxazole was selected as it represents a frequently used combination antibiotic, is renally cleared, and is used for the management of bacterial infections in the HBV patient population

4.2.3.2 Recommended drugs for future drug-drug interaction studies with ADV DP

The sponsor will be asked to conduct additional drug-drug interaction studies with representative agents from different therapeutic classes. The representative drugs will be selected on a mechanistic-basis, to evaluate ADV's interaction potential with drugs that may be coadministered with ADV DP. Examples of such compounds include, antiretroviral agents, analgesic agents, and immunosuppressive agents (e.g. tacrolimus and cyclosporine). The results from a tacrolimus/cyclosporine-ADV-DP to evaluate the CYP-3A4 induction potential of ADV have not yet been provided by the sponsor.

5. What are the general Biopharmaceutical characteristics of the adefovir dipivoxil formulations?

5.1 BCS Classification

ADV-DP is classified as a BCS Class 3 drug because it has a high solubility and low permeability. Solubility and permeability (Caco-2 cells) data regarding the BCS classification were reviewed in

5.2 Biowaiver Information

The composition, dissolution and bioavailability data submitted indicate that a bioequivalence study will not be required for the new 10 mg tablet, because the pharmacokinetics of ADV are not likely to be influenced by the small change in shape (physical properties) between the commercial formulation and the clinical trial formulation. Thus, a biowaiver for an *in vivo* bioequivalence study was granted to the sponsor, prior to NDA submission.

5.2.1 CMC and Bioavailability Information

As shown in Table I, the commercial tablet formulation has the same composition as the clinical trial formulation, but varies slightly in shape. The change in shape does not appear to conform to a specific manufacturing level change, thus the spirit of principles of *SUPAC IR* could not be directly applied. However, the Chemistry reviewer agrees that the formulation change is minor and does not raise any concerns from the chemistry manufacturing and controls perspective (CMC). It is noted that the sponsor used the proposed commercial formulation in a food effect study (Study GS-00-476), therefore supportive exposure data are available with the proposed commercial formulation. PK exposure data from the food effect study were consistent with PK data obtained from other studies, thereby supporting the decision to grant the biowaiver.

Additionally, results from pharmacokinetic study (Study GS-99-457) using 60 mg ADV formulations with compositions and geometries that were more varied than those with the 10 mg tablets indicate that changes in geometry did not affect bioequivalence or ADV PK. The sponsor provided dissolution data

(proposed dissolution method) that showed that tablet shape did not affect dissolution behavior of the 10 mg tablets (commercial or clinical trial formulation).

Table I: Composition and Physical Characteristics of Adefovir Dipivoxil Formulations

	% (w/w)	
	Adefovir Dipivoxil 10 mg Formulations	
Composition	Clinical Trial	Proposed Commercial
Adefovir dipivoxil		
Pregelatinized starch		
Croscarmellose sodium		
Lactose monohydrate		
Talc		
Magnesium stearate		
Tablet Weight (mg)	150	150
Physical Attributes		
Diameter (mm)		
Surface Area (inches ^{2})		
Volume (inches ^{3})		
Surface Area/Volume (inches $^{-1}$)		
Shape		

6 What bioanalytical methods were used to quantify ADV concentrations in plasma and urine?
A validated bioanalytical method was used to assay ADV plasma and urine samples. The assay was acceptable and had the following characteristics across all studies:

Parameter		Comment
Linear range		Satisfactory
Accuracy		Satisfactory
Precision		Satisfactory
LLOQ		Satisfactory
Stability (freeze-thaw)		Satisfactory
Specificity		Satisfactory

7. What are the proposed Dissolution Method and Specification?
The proposed dissolution method and specification for adefovir dipivoxil tablets are acceptable.

USP Dissolution Apparatus 2, Paddle at 50 rpm
Dissolution Medium 600 mL of 0.01 N HCl at 37 ± 0.5 ^{o} C
Sampling times are 5, 10, 20, 30, 45, and 60 minutes
Q = NLT in 30 minutes

Background
As stated previously, ADV-DP is a BCS Class 3 drug. ADV DP has a pKa of 3.75 and an intrinsic solubility of 0.34 mg/mL, suggesting that ADV DP will be highly soluble in the typically tested pH range and media.

Methodology Highlights

1) Samples were collected at 10, 20, 30, and 45 minutes to generate dissolution profiles.
2) ADV DP concentrations are determined by UV-spectroscopy
3) Parameters evaluated in the dissolution studies were the pH of the medium and effects of drug product manufacturing processes.

pH media tested

Medium	pH
[redacted]	
[redacted]	
[redacted]	

The sponsor indicated that for the 10 mg tablet, medium volume and paddle speed (low) were fixed at 600 mL and 50 rpm . Sink conditions were maintained in a 600 mL volume, and this volume was appropriate for the quantitative step of the method.

Summary of Dissolution Results

1) Data were consistent, with CV generally less than 10 %.

2) The dissolution data indicate that at 30 minutes the mean percent dissolved is greater than 95 % over the pH range evaluated. However, there was a trend of a slight decrease in amount of drug dissolved as media pH increased.

3) Tablet dissolution was not affected by several processes including, [redacted]

Rationale for Method Selection

The medium with pH 2 was selected because it is representative of gastric fluid, yet provides some degree of discriminatory power to variability in the manufacturing process. Additionally the relatively low paddle speed (50 — rpm) may minimize the effect of paddle speed on dissolution, which may unduly affect the dissolution of a highly soluble drug. The sponsor's rationale for the method selection appears valid.

APPEARS THIS WAY
ON ORIGINAL

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-449	Brand Name	Not determined
OCPB Division (I, II, III)	Division III	Generic Name	Adefovir dipivoxil
Medical Division	Antiviral Drug Products	Drug Class	Nucleotide reverse transcriptase inhibitor
OCPB Reviewer	Robert O. Kumi	Indication(s)	Hepatitis B in adults
OCPB Team Leader	Kellie Reynolds	Dosage Form	Tablet
		Dosing Regimen	10 mg once daily
Date of Submission	03/20/2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	07/20/2002	Sponsor	Gilead Sciences
PDUFA Due Date	09/20/2002	Priority Classification	Priority
Division Due Date	09/13/2002		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
I. Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				Assessment possible using historical data
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:	X			
Subpopulation studies -				
ethnicity:				Analyses conducted
gender:				Analyses conducted
pediatrics:				
geriatrics:				Analyses conducted
renal impairment:	X			
hepatic impairment:	X			
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				No formal analyses, but concept used for dose selection. Viral kinetic data
Phase 3 clinical trial:				

Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				Comparison to historical IV data at higher dose
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			
Literature References				
Total Number of Studies	[redacted]			

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	Potential induction- relation to tacrolimus/cyclosporine Dissolution information for commercial lots
QBR questions (key issues to be considered)	**Is the dosage adjustment for subjects with impaired renal function appropriate?**	
Other comments or information not included above	**Drug was previously submitted for HIV indication (60 mg dose), but the submission was not approved. Clinical Pharmacology and biopharmaceutics information from HIV-indication will be useful during review of this NDA for Hepatitis B indication.**	
Primary reviewer Signature and Date	**Robert O. Kumi, Ph.D.**	
Secondary reviewer Signature and Date	**Arzu Selen, Ph.D.**	

CC: NDA 21-304, HFD-850 (Lee), HFD-530 (Holloman), HFD-880 (Reynolds, Lazor, Selen), CDR

APPENDIX: Clinical Pharmacology and Biopharmaceutics Individual Study Review

Study Title:	An Open-Label Phase 1/2 Study of the Pharmacokinetics, Safety, and Antiviral Activity of Adefovir Dipivoxil in Nucleoside Treatment-Naive HBV-Infected Patients
Study No.:	GS-00-472
Study Period:	July 23, 2001 (First patient enrolled post-Amendment 2)- August 28, 2001(Last patient observation)
Study Centers:	4 Centers in the United States, 2 Centers in France
Report Date:	December 5, 2001

PK-related Objectives

- To characterize the pharmacokinetic profile for a single dose and at steady state following multiple doses during 7 days of treatment with a daily dose of 10 mg adefovir dipivoxil (ADV) in HBV infected patients.
- To assess the safety of adefovir dipivoxil 10 mg over 7 days

Study Design

This is an open-label 7-day pharmacokinetic and pharmacodynamic study to be followed by 47 weeks of continued treatment with 10 mg daily of adefovir dipivoxil. HBV-infected subjects received multiple doses of adefovir dipivoxil. Adefovir PK in plasma were determined in all patients over a 24-hour period on Day 1-2, and over a 12-hour period on Day 7. Subjects fasted on PK sampling days.

Subjects

14 patients with chronic HBV enrolled in the study. All patients received one dose once daily for all 7 days of the pharmacokinetic study. No patients discontinued prematurely

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics are summarized in Table I. There was a fairly even race distribution in the study, and a greater number of males participated in the study than females.

Demographics and Baseline Characteristics

Characteristic	n
Gender	9 male and 5 female
Age (Years)	
Mean ± SD	40.1 ± 14.1
Range	23.0–68.0
Race	5 Caucasian, 4 Asian, and 5 Black
Weight (kg)	
Mean ± SD	88.0 ± 31.4
Range	43.1–143.8
ALT	
Mean ± SD	93.8 ± 59.8
Median	79.0

Formulations

Adefovir dipivoxil, batch numbers D906A2, D010A1, D906A3, and D004A1

L-carnitine*, 250 mg/day for patients whose carnitine levels fall below the lower limit of normal range, batch number G945

* carnitine levels may be decreased due to sequestration by pivalic acid that is released from adefovir dipivoxil.

Pharmacokinetics:
The following ADV PK parameters were determined: C_{max}, T_{max}, C_{last}, C_{min}, T_{min}, T_{last}, K_{el}, $T_{1/2\,\lambda z}$, AUC_{0-t}, $AUC_{0-\tau}$, $AUC_{0-\infty}$, % AUC extrapolated, V_z/F, CL/F, F (%), CL_{renal}, % dose eliminated

Pharmacokinetic Sampling Schedule:
Collection of blood samples: 0/pre-dose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dose on day 1–2. Blood collection time points for pharmacokinetics on Day-7 stopped with the collection at hour 12 post-dose.
Collection of urine samples: 0/pre-dose void, 0-4, 4-8, 8-12 and at 12-24 hours on day 1-2.

Safety:
Occurrence of adverse events, changes from baseline in standard chemistry and hematology laboratory parameters, and changes in specific laboratory values related to renal function.

Statistical Methods: ADV PK measures were evaluated using standard PK-statistical methods.

Assay/Analytical Method
A validated [redacted] bioanalytical method [redacted] was used to assay ADV samples. The assay was acceptable and had the following characteristics:

Parameter	[redacted]	Comment
Linear range		Satisfactory
Accuracy		Satisfactory
Precision		Satisfactory
LLOQ		Satisfactory
Stability (freeze-thaw)		Satisfactory
Specificity		Satisfactory

Pharmacokinetic Results:
Adefovir was rapidly absorbed (median $T_{max} < 2$ hr) after the first dose of adefovir dipivoxil 10 mg. After C_{max} was achieved, concentrations declined in a biexponential manner. Plasma concentrations were quantifiable for 24 hours after dosing in most patients. The sponsor estimated a median oral bioavailability (58 %) of adefovir from adefovir dipivoxil 10 mg using historical IV data as a control. The IV data was from a study in a cohort of HIV-infected patients administered 1 mg/kg of intravenous adefovir. Although this cross-study/population comparison is not ideal, it provides an estimate of relative oral bioavailability.

Table I: Summary of ADV Pharmacokinetic Parameters following adefovir dipivoxil 10 mg single dose

	$AUC_{0-\infty}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{½\lambda z}$ (hr)	CL/F (mL/hr/kg)
Mean ± SD	233 ± 66	19.5 ± 6.1	NA	7.5 ± 1.7	454 ± 154
Minimum	[redacted]				
Maximum					
N	11	14	14	14	14

NA = not applicable

Based on comparisons (Tables I and II) of AUCs, half-lives and apparent clearance, the PK of adefovir following multiple dosing (Day 7) were similar to those following a single dose (Days 1-2). The sponsor conducted the following analyses to demonstrate that ADV PK were similar between multiple-dose and single dose administration:

1. Geometric mean $AUC_{0-\delta}$ on Day 7 was 203.51 ng•hr/mL compared with an AUC_{0-} of 210.15 ng•hr/mL (p = 0.4996, paired t-test) on Day 1-2,
2. Geometric mean C_{max} on Day 7 and Day 1-2 were 18.33 and 17.47 ng/mL, respectively (p = 0.4830, paired t-test).
3. Using the Wilcoxon signed rank test the following p values were associated with the PK measures: Apparent clearance, CL/F (p = 0.6257) renal clearance (p = 0.9505), and half-life (p = 0.6257) of adefovir on Day 7 versus Day 1-2.

Table II: Summary of ADV PK Parameters on Day 7 following adefovir dipivoxil 10 mg once daily dosing

Day 7	$AUC_{0-\delta}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{½\lambda z}$ (hr)	CL/F (mL/hr/kg)
Mean ± SD	216 ± 79	19.7 ± 8.2	NA	8.2 ± 3.5	471 ± 154
Minimum					
Maximum					
N	14	14	14	14	14

In sum, the single- and multiple-dose PK data indicate the lack of accumulation of drug and unchanged ADV PK after multiple doses compared with those following a single dose of adefovir dipivoxil. Furthermore, oral administration of adefovir dipivoxil 10 mg once daily to patients with chronic HBV infection resulted in a predictable concentration-time profile and pharmacokinetics that were similar to those observed in healthy subjects.

Urinary PK

Urinary recovery of unchanged drug was approximately 42 % (median) over a twenty-four collection period and was consistent with the estimated oral bioavailability (F = 58 %) derived from plasma data. It should be noted that for a drug that is primarily renally eliminated, the urinary recovery provides a good estimate of oral bioavailability. The renal clearance of adefovir was substantially greater than glomerular filtration rate, indicating a greater contribution of net tubular secretion relative to reabsorption (if any) to the excretion of adefovir. This finding was also observed in healthy volunteers.

As shown in Table III, the ADV urinary excretion parameters were similar on Day 1 and Day 7.

Table III: Urine Adefovir Pharmacokinetic Parameters

	Day 1-2	Day 7
Median % Dose Recovered	41.88	35.56
Median CL_{renal} in mL/hr/kg	164 (37 – 232)	154 (84 – 340)
Median ADV Urinary Excretion in mg	2.28 (0.90 – 2.93)	1.93 (0.96 – 3.01)

Safety Results (sponsor's summary):

No deaths or other serious adverse events were reported during the initial 7 day pharmacokinetic portion of this 48 week study. No patient discontinued study treatment because of an adverse event. All reported adverse events were of mild or moderate severity. Oral administration of adefovir dipivoxil 10 mg once daily for 7 days appeared to be safe and generally well tolerated in these adult patients with chronic HBV.

Pharmacokinetic Conclusions

- The pharmacokinetics of a 10 mg dose of adefovir dipivoxil are comparable in patients with chronic HBV and healthy subjects.
- The single-dose and multiple-dose (steady-state) pharmacokinetics of 10 mg once daily dose of adefovir dipivoxil are similar, and single-dose pharmacokinetics (PK) can predict multiple dose PK
- No accumulation occurred upon multiple dosing

- The estimated relative oral bioavailability of adefovir from a 10 mg dose of adefovir dipivoxil was approximately 60 percent.
- Adefovir is primarily renally eliminated, and excretion is by a combination of glomerular filtration and net tubular secretion.

Safety Conclusions
Oral administration of adefovir dipivoxil 10 mg once daily for 7 days appeared to be safe and generally well tolerated in these adult patients with chronic HBV.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Study Title:	A Phase 1, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics of Adefovir Dipivoxil in Subjects with Normal and Impaired Renal Function
Study No.:	GS-00-473
Name of Test Drug:	Adefovir Dipivoxil
Study Duration	04/2001 – 10/2001
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94044 USA
Investigators:	[redacted]
Study Centers:	[redacted]

Rationale for the Current Study

Following oral administration, adefovir dipivoxil (ADV DP) is converted to adefovir (ADV) which is eliminated renally from the body through a combination of glomerular filtration and active tubular secretion. ADV has exhibited mild to severe nephrotoxicity at doses greater than or equal to 30 mg once daily given. Therefore it is important to determine the ADV exposure in subjects receiving ADV DP

Objectives

- To evaluate the pharmacokinetics of adefovir following administration of adefovir dipivoxil 10 mg in subjects with normal renal function and varying degrees of renal function impairment, including subjects with ESRD undergoing hemodialysis.
- To develop dosing guidelines for patients with chronic HBV who have renal function impairment.
- To evaluate the safety of adefovir dipivoxil 10 mg in subjects with normal renal function and in subjects with varying degrees of renal function impairment.

Study Design:

An open label, single dose (10 mg adefovir dipivoxil), parallel study design was employed for non-hemodialysis groups. Subjects undergoing hemodialysis received two adefovir dipivoxil doses: one dose before hemodialysis and one dose after hemodialysis, separated by 1 week.

Subjects:

In all, 41 subjects were evaluable. There were five study groups. These groups were stratified based on calculated creatinine clearance using the Cockroft-Gault method, and mirrored the scheme outlined in the *Guidance for Industry* that addresses renal impairment studies. Each group had 7 to 10 subjects. Demographic characteristics of the subjects who participated in the trial are summarized in the Appendix. In this study, enrolment was open to subjects between the ages of 18 to 70, however, the majority of subjects were above 35 years old, and the mean age in all groups was above 40 years. It should be noted that the effects of age or gender on ADV PK have not been previously defined; thus, their potential role in the evaluation of renal impairment is unknown.

Dosing Procedures

All study subjects fasted from midnight on the night before their scheduled study visit (Day 1). With the exception of water, subjects continued to fast until after the 4 hour postdose blood draw (12 hours of fasting), after which a standardized meal was provided. For hemodialysis subjects, the high flux hemodialysis session began two hours after the drug was administered. Approximately one week later, after a minimum of three hemodialysis sessions, hemodialysis subjects returned for the second dose of study drug, which was administered on the day after a hemodialysis session.

Formulation
Adefovir dipivoxil 10 mg; Lot No. D010A1

Blood Sampling
- Non-dialysis patients-Serial blood samples were collected from predose (0 hr) to 96 hours postdose: 0/predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours
- Dialysis patients- During dialysis, serial blood samples were collected from predose to 48 hours post dose: 0/predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 6.5, 7, 8, 12, 24, 36, and 48 hours
- Dialysis patients- After dialysis, serial blood samples were collected from predose to 30 hours post dose: 0/predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 30 hours

Urine Sampling
Non-dialysis patients- Urine samples were collected at various collection intervals from predose (void) to 96 hours post dose: 0/predose void, 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–72, and 72–96 hours

Assay/Analytical Method
A validated [redacted] bioanalytical method was used to determine adefovir concentrations in plasma samples. The method was validated by [redacted] and was linear over a range of [redacted] with a lower limit of quantitation of [redacted] The method was highly sensitive and specific to adefovir with accuracy and precision deviations of less than 10.0 % and 4.9 % (percent bias), respectively.

Pharmacokinetic Analyses
Standard PK measures were calculated using a noncompartmental approach (WinNonlin®).

Pharmacokinetics Results:
Data were available from 41 subjects however, data from two subjects were excluded in subsequent PK analysis because one subject's extrapolated AUC % exceeded 30 % and the exposure in the other subject (CL_{cr} < 10 mL/min) was inconsistent with exposures in other subjects with severe renal impairment.

Comment
Exclusion of these data is acceptable, because inclusion of these data may skew the data and lead to inaccurate interpretation of PK results.

The PK of ADV in subjects with varying renal function are presented in Table I. The pharmacokinetics of adefovir following administration of adefovir dipivoxil 10 mg in normal subjects in this study were similar to those in previous studies (GS-00-474, GS-00-475, GS-00-476, and GS-00-472). This finding suggests that the control (normal renal function) group used in the renal impairment study is acceptable.

As expected, the pharmacokinetics of adefovir varied with changing renal function, because ADV is primarily renally eliminated. Only subjects with mild renal impairment had essentially similar pharmacokinetics relative to normal subjects; although these patients with mild renal impairment had slight reductions in adefovir CL/F and CL_{renal} compared to normal subjects. Despite these alterations, it is reasonable not to dose-adjust patients with mild renal impairment because only one tablet strength is available. Adefovir pharmacokinetics were substantially altered in subjects with moderate and severe renal impairment compared to the control group. The mean AUC in subjects with moderate and severe renal impairment were 2 and 5 fold higher, respectively, than the mean AUCs in subjects with CL_{Cr} > 50 mL/min. This finding of increased exposure suggests that subjects with moderate and severe impairment will require dosage adjustments.

Table I: Single Dose Adefovir Pharmacokinetic Parameters in Subjects With Varying Degrees of Renal Function

	Renal Function			
	Normal (N = 7[a])	Mild Impairment (N = 8)	Moderate Impairment (N = 7)	Severe Impairment (N = 10)
Typical CL_{Cr} range	> 80 mL/min	50 – 80 mL/min	30 – 49 mL/min	< 30 mL/min
C_{max} (ng/mL)				
Mean ± SD	18 ± 3	22 ± 4	28 ± 9	52 ± 10
Range				
$AUC_{0-\infty}$ (ng•hr/mL)				
Mean ± SD	201 ± 41	266 ± 56	455 ± 176	1244 ± 629
Range				
CL/F (mL/min)				
Mean ± SD	469 ± 99	356 ± 86	237 ± 118	92 ± 51
Range				
CL_{renal} (mL/min)				
Median	211.20	149.23	85.85	34.83
Range				
$T_{½\lambda z}$ (hr)				
Median	7.01	7.16	7.44	14.70
Range				
$CL_{last\ (96\ hr)}$ (ng/mL)				
Median	1.56	1.40	1.96	1.45
Range				
T_{max} (hr)				
Median	1.00	1.00	1.50	8.00
Range				
CL_{Cr} (mL/min)				
Mean ± SD	109 ± 25	66 ± 16	40 ± 9	18 ± 6

a The extrapolated % $AUC_{0-\infty}$ for subject 1085-0001 was greater than 30 %; therefore, in accordance with the protocol, data from this subject were not included in the summary statistics. For remaining subjects individual AUC % extrapolated was < 23 %, with most subjects having < 10 % AUC extrapolated

^ Comment on individual CL_{Cr} and Placement in groups

In an amendment to this NDA, the sponsor provided their rationale for placing certain subjects in renal impairment groups that were not anticipated based on the subjects CL_{Cr} values. The incorrectly assigned subjects were as follows: one subject with CL_{Cr} = 46 mL/min and another subject with CL_{Cr} = 96 mL/min were in the mild renal impairment group, and one subject with CL_{Cr} > 50 mL/min was included in the moderate renal impairment group. Because, subsequent PK subgroup analyses appropriately assigned subjects based on CL_{cr}, the incorrect placement of these subjects in the summary tables was acceptable.

Urinary Excretion

Urinary excretion pharmacokinetic parameters for adefovir following administration of ADV DP are summarized in Table II. The total urinary excretion of ADV was estimated from the sum of amounts eliminated over the 96-hour urine collection period. Generally, the amount of drug recovered in the urine decreased, with decreasing CL_{Cr} (CL_{renal}). This finding is expected because ADV is eliminated primarily by the renal route.

Adefovir Urinary Pharmacokinetic Parameters in Subjects With Normal Renal Function and Those With Mild, Moderate, or Severe Renal Impairment (Median Values) after single dose of adefovir dipivoxil 10 mg

	Renal Function			
	Normal (N = 7*)	Mild impairment (N = 8)	Moderate Impairment (N = 7)	Severe Impairment (N = 10)
Urinary Excretion (mg)				
Median	2.69	2.38	2.10	1.93
Range				
% Dose Eliminated				
Median	49.40	43.67	38.59	35.40
Range				

* The extrapolated % $AUC_{0-\infty}$ for subject 1085-0001 was greater than 30 %; therefore, in accordance with the protocol, data from this subject were not included in the summary statistics.

Adefovir Pharmacokinetics in Subjects Receiving Hemodialysis

Hemodialysis efficiently removed adefovir from the plasma. The estimated median extraction efficiency and median $CL_{dialysis}$ were 63 % and 133.79 mL/min, respectively. ADV-DP was administered on two occasions (sessions) to patients requiring hemodialysis, specifically, intra- and inter-dialysis sessions.

Intradialysis Session

Subjects with ESRD requiring hemodialysis experienced substantially higher systemic adefovir exposures relative to subjects with CL_{Cr} > 50 mL/min. Following oral administration of adefovir dipivoxil 10 mg, plasma concentrations of adefovir increased until the start of dialysis (2 hours post dose). During the 4-hour hemodialysis session, median plasma ADV concentrations declined with time and ADV at the end of the hemodialysis period (5 – 6 hours post dose) concentrations were comparable to the C_{max} observed in normal subjects (18.16 ng/mL). Dialysis removed approximately 35 % of administered drug and the median plasma hemodialysis clearance ($CL_{dialysis}$) was 133.79 mL/min. However, the $CL_{dialysis}$ value and the k_{ed} values should be interpreted cautiously because there appeared to be a substantial delay in adefovir absorption that may mask the elimination phase in patients with profound renal impairment. Thus, the estimated k_{ed} and percent of the dose removed by hemodialysis in these subjects is likely to be underestimated.

Comment

The sponsor suggests that the k_{ed} values are likely to be underestimated, and it appears that the sponsor uses this premise for making dosing recommendations related to monitoring of HBV levels (see Dosage Adjustment in Patients undergoing hemodialysis or with CL_{cr} < 10 mL/min).

After dialysis was complete (> 6 hours post dose), adefovir plasma concentrations exceeded pre-hemodialysis concentrations (< 2 hours post dose) in most subjects (7 of 8 subjects). In the post-dialysis period, ADV concentrations increased to a median C_{max} of 56.72 ng/mL and remained at a plateau for the remainder of the study period (30 hours post dose), indicating the absence of an extrarenal route of elimination for the drug. No terminal elimination phase (λ_z) of adefovir in plasma was observed.

Interdialysis Session

Subjects in this group underwent a varying number of total (including the intradialysis visit) hemodialysis sessions: 3 sessions (n = 1), 4 sessions (n = 5), or 5 sessions (n = 2), prior to the second dose of adefovir dipivoxil. The difference in the number of sessions did not appear to significantly alter the predose plasma concentrations. All subjects had quantifiable concentrations of adefovir in plasma at the predose collection time point of the interdialysis session. The median predose ADV concentration was 3.13 ng/mL ( ). This finding suggests that drug accumulation is likely to occur in

these patients. In the absence of dialysis, oral administration of adefovir dipivoxil 10 mg, resulted in ADV plasma concentrations that increased to a median C_{max} value of 82.81 ng/mL (≈ 4x greater than in normal subjects). After achieving C_{max}, little change occurred in plasma concentrations, indicating no significant extrarenal route of elimination of adefovir. All subjects had quantifiable concentrations of adefovir at the last measured time point (T_{last}, 30 hours), with a median C_{last}, of 71.57 ng/mL. The AUC over the dosing interval (2100 nghr/mL) was several fold greater than the AUC in normal subjects. An ADV terminal elimination phase (λ_z) was not observed.

Comment on Dosing Implications

With ESRD, there is no concern for nephrotoxicity as the kidneys of these individuals are essentially non-functional. However, it is not clear if high sustained or intermittent ADV exposures (concentrations) will adversely effect other organs or systems. The Medical Officer indicated that there may be some concern for depletion of phosphates and other markers of ADV toxicity.

Derivation of Dosing Algorithm: Relationships between Adefovir PK and Renal Function

The dosing algorithm was derived by following the two sequential steps outlined in the *Guidance for Industry* (Renal Impairment Studies):

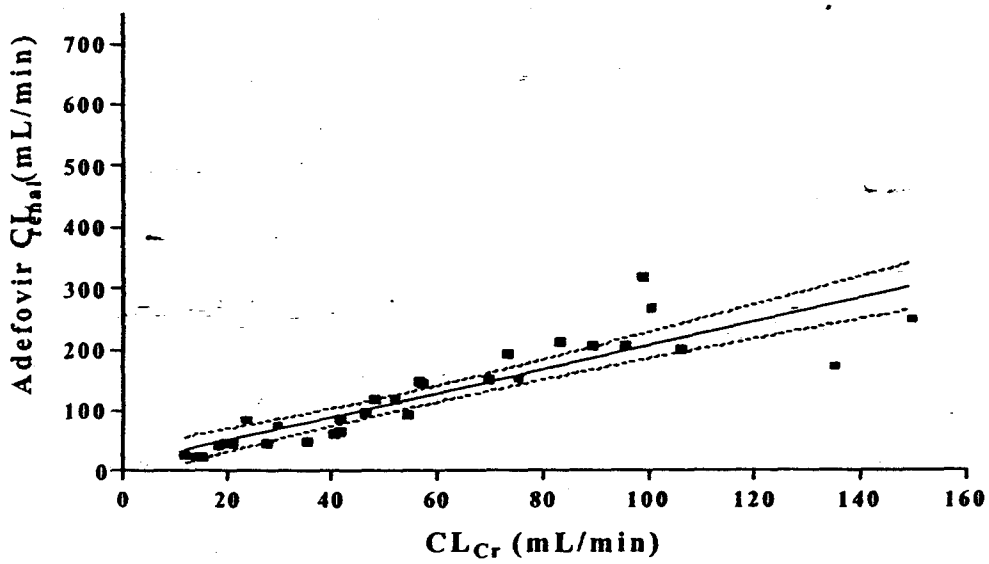
- Linear regression analyses were performed to evaluate adefovir pharmacokinetics in relation to renal function. Specifically, metrics of ADV clearance (CL_{renal} and CL/F) and exposure (C_{max} and $AUC_{0-\infty}$) were compared with renal function (CL_{Cr} by Cockcroft-Gault method).
- Simulation was conducted to predict expected ADV exposure upon multiple dosing for various dosing intervals

Linear Regression Analyses

1a) CL_{Cr} and CL_{renal}

Figure 1 depicts the relationship between CL_{Cr} and CL_{renal}. The relationship between CL_{renal} and CL_{Cr} was linear over the CL_{Cr} range of 10 to > 80 mL/min. This finding indicates that changes in adefovir renal excretion are predicted by the degree of renal function impairment, based on CL_{Cr}. It is noted that ADV CL_{renal} was approximately twice the calculated CL_{Cr} (based on slope 1.93) in all stages of renal dysfunction, suggesting that net tubular secretion of ADV is preserved despite progressive renal damage.

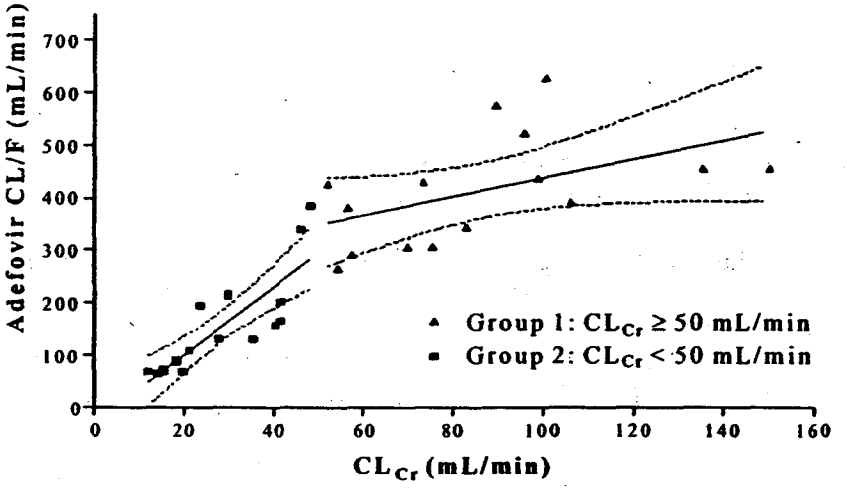
Figure 1: Relationship between CL_{cr} and CL_{renal}



1b) CL_{Cr} and ADV exposure metrics

The relationship between CL/F and CL_{Cr} was characterized by two distinct lines, with two different slopes (Figure 2).

Figure 2: Relationship Between Adefovir Apparent Clearance (CL/F) and Calculated CL_{Cr} (mL/min) (Linear Regression With 95 % Confidence Band)



These two lines correspond to subjects with CL_{Cr} 50 mL/min (normal to mild renal impairment) and CL_{Cr} < 50 mL/min (moderate to severe renal impairment). The slope of the line in subjects with CL_{Cr} < 50 mL/min was approximately 4 times steeper than that for subjects with CL_{Cr} < 50 mL/min. The differences in the slopes for the two groups suggest that the two groups exhibit different ADV PK. Systemic adefovir exposure measures ($AUC_{0-\infty}$, C_{max}) versus CL_{Cr} yielded two different slopes, corresponding to the CL_{Cr} groups previously described (plot not shown). It is noted that AUC and C_{max} appear to be highly correlated.

1c) Twenty-four hour CL_{Cr} with CL_{CrU}

Data from urine samples were used in an attempt to establish a correlation between CL_{Cr} with CL_{CrU}. However, this analysis was flawed in that urine samples were not representative of a true 24-hour urine collection. Due to the limitation in the study design, this analysis was not reviewed further.

2. Simulations

The simulations were carried out in two phases:

a) prediction of ADV PK upon multiple dosing for once daily administration and

b) prediction of ADV PK multiple dose according to the dosing intervals proposed.

Because there is only one ADV DP dosage strength available, dosage adjustments have to made by changing the dosing interval or frequency.

Assessment of Compartmental Model

Prior to conducting simulation step a, the sponsor compared the results of compartmental analyses to noncompartmental analyses to assess the utility of compartmental analyses for subsequent simulation. Plasma concentration-time data were used to estimate ADV PK parameters (k_a, k_e, and V/F), stratified by CL_{Cr} using compartmental analyses (WinNonlin®). The sponsor notes that non-hemodialysis subjects (n = 1) with CL_{Cr} < 10 mL/min appear to be described by a different linear relationship; consequently, PK simulations for this group were not performed, and extrapolation of the results to CL_{Cr} values < 10 mL/min is not recommended. However, the sponsor has proposed that non-hemodialysis patients