

with  $CL_{Cr}$  should be treated (dosed) similarly to patients with ESRD. This approach does not seem reasonable, because there are insufficient data to support the proposed 10 mg once weekly ADV DP use in these patients.

Characteristics of the compartmental model were as follows:

1 compartmental model, first order input, and elimination rate constants with no lag time. The Gauss-Newton Method of minimization of sums of squares and convergence criteria 0.0001.

Table III: Comparison of Modeling Results (1-CM) of Predicted Median Adefovir Concentration-Time Values and Observed Noncompartmental Analysis (NCA)

Model	Renal Function					
	$CL_{Cr} \geq 50$ mL/min (N = 15)		$CL_{Cr}$ 20 to 49 mL/min (N = 10)		$CL_{Cr}$ 10 to 19 mL/min (N = 6)	
	NCA <sup>c</sup>	1-CM <sup>d</sup>	NCA <sup>c</sup>	1-CM <sup>d</sup>	NCA <sup>c</sup>	1-CM <sup>d</sup>
AUC <sub>0-∞</sub> (ng·hr/mL)	214	237	509	537	1317	1332
C <sub>max</sub> (ng/mL)	20.1	18.1	35.3	32.2	54.3	51.2
T <sub>max</sub> (hr)	1.00	1.31	1.50	1.98	8.00	3.95
T <sub>1/2λz</sub> (hr)	6.53	8.15	7.98	10.09	16.2	15.03

c NCA = noncompartmental analysis.

d 1-CM = one compartment model.

From Table III it is clear that compartmental modeling produced PK median estimates that were comparable to PK estimates obtained with NCA. In general, the CM produced lower C<sub>max</sub> and AUC than NCA, and predicted a much shorter T<sub>max</sub> for patients with severe renal impairment.

**Comment:**

*The sponsor's overall modeling approach appears acceptable. However, it is unclear if the sponsor attempted to use a lag time model or alternative (non-linear) model that may have improved the modeling, especially in subjects with severe renal impairment. The model selection has a significant impact on the ensuing simulations; however, insufficient data are available to validate alternative models, such as models with nonlinear input/elimination.*

**Simulations based on once daily dosing to achieve steady state**

Using the 1-CM derived rate and volume of distribution constants, adefovir plasma concentration-time curves (figure 3) and PK exposure measures were predicted over 7 days of once daily dosing to illustrate steady state pharmacokinetics for each stratum of renal function (Table IV).

Predicted Adefovir Steady State Concentration-Time Profiles Following Once Daily Dosing by Renal Function Defined by calculated creatinine clearance

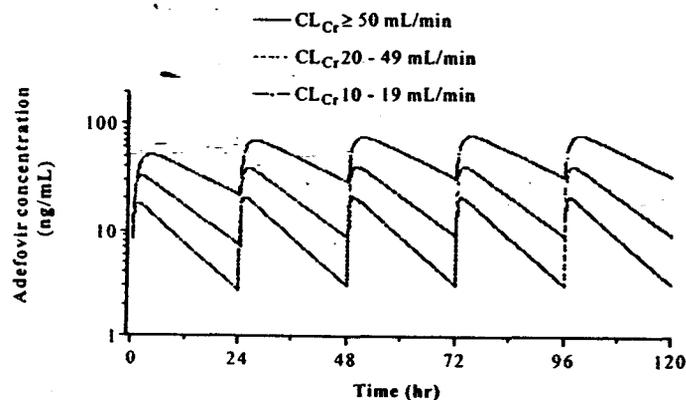


Table IV: Predicted Adefovir Steady State Pharmacokinetics Following Once Daily Dosing (10 mg ADV DP)

	Renal Function			
	CL <sub>Cr</sub> 20 to 49 mL/min		CL <sub>Cr</sub> 10 to 19 mL/min	
	1-CM	% Ratio <sup>a</sup>	1-CM	% Ratio <sup>b</sup>
AUC <sub>0-∞</sub> (ng·hr/mL)	537	226 %	1332	561 %
C <sub>max</sub> (ng/mL)	40.2	193 %	78.2	375 %
C <sub>trough</sub> (ng/mL)	9.08	295 %	32.0	1039 %

a CL<sub>Cr</sub> 20 to 49 mL/min: CL<sub>Cr</sub> ≥ 50 mL/min. b CL<sub>Cr</sub> 10 to 19 mL/min: CL<sub>Cr</sub> ≥ 50 mL/min.

1-CM = 1 compartment model; Median (minimum, maximum) predicted values from one compartmental analysis.

Based on the simulation, negligible accumulation is expected in subjects with normal renal function or mild renal impairment because ADV has a short terminal elimination half-life (< 9 hours) relative to the 24 hour dosing interval. Therefore, the sponsor indicated that subjects from these two groups were combined into one group for all subsequent analyses. This approach appears reasonable based on the available information. As shown in Table IV, subjects with moderate and severe renal impairment will have significant accumulation (C<sub>max</sub>, C<sub>min</sub>, AUC) of adefovir relative to normal subjects following once daily dosing of adefovir dipivoxil 10 mg. The predicted adefovir C<sub>trough</sub> in these two groups was more than 7-fold higher than the trough concentrations in normal, unimpaired subjects. These findings indicate that subjects with moderately and severely impaired renal function should not be dosed on a once daily basis.

*Simulations based on alternative dosing intervals to achieve steady state*

Simulations were conducted for different dosing intervals to obtain an acceptable dosing regimen for subjects with CL<sub>Cr</sub> < 50 mL/min. Ideally, this regimen should limit drug accumulation, yet provide C<sub>trough</sub> that were comparable to C<sub>trough</sub> obtained in normal subjects. This approach is reasonable as safety and efficacy will be potentially optimized. At steady state, AUC<sub>0-τ</sub> remains constant and is equal to the AUC<sub>0-∞</sub> observed following a single dose, if renal function (PK) are time-independent. Thus, in subjects with CL<sub>Cr</sub> of 20 to 49 mL/min or CL<sub>Cr</sub> of 10 to 19 mL/min, a single dose of adefovir dipivoxil 10 mg resulted in a fixed AUC<sub>0-τ</sub> of 537 or 1332 ng·hr/mL, respectively (median 1-CM predicted values). These fixed AUC values were used in simulations over the following dosing intervals: once daily (every 24 hours), every two days (every 48 hours), every 3 days (every 72 hours), and every 7 days (every 168 hours) for subjects with varying CL<sub>Cr</sub>. The most appropriate dosing intervals, using the available 10 mg tablet, were every 48 hours for subjects with CL<sub>Cr</sub> of 20 to 49 mL/min and every 72 hours for subjects with CL<sub>Cr</sub> of 10 to 19 mL/min (Table V).

Figure 4: Simulated Adefovir Steady State Concentration-Time Profiles Following Dose Interval Adjustment by Renal Function Defined by calculated creatinine clearance

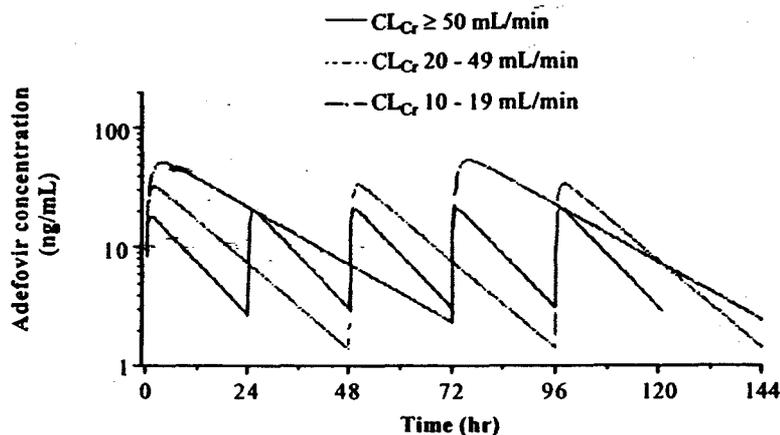


Table V: Simulated Adefovir Steady State Pharmacokinetics Following Dose Interval Adjustment

	Degree of Renal Impairment Based on Creatinine Clearance			
	CL <sub>Cr</sub> = 20 to 49 mL/min (every 48 hours)		CL <sub>Cr</sub> = 10 to 19 mL/min (every 72 hours)	
	Simulated	% Ratio <sup>a</sup>	Simulated	% Ratio <sup>b</sup>
AUC <sub>0-τ</sub> (ng·hr/mL)	537	113	1332	187
C <sub>max</sub> (ng/mL)	33.5 (16.1–48.5)	161	53.2 (48.2–59.6)	255
C <sub>trough</sub> (ng/mL)	1.42 (0.88–5.21)	52	2.37 (0.43–3.33)	87

- a Ratio of simulated parameters obtained over a 48-hour dosing interval in subjects with CL<sub>Cr</sub> 20 to 49 mL/min to the simulated parameters obtained over two 24-hour dosing intervals (48 hours) in subjects with CL<sub>Cr</sub> ≥ 50 mL/min
- b Ratio of simulated parameters obtained over a 72-hour dosing interval in subjects with CL<sub>Cr</sub> 10 to 19 mL/min to the simulated parameters obtained over three 24-hour dosing intervals (72 hours) in subjects with CL<sub>Cr</sub> ≥ 50 mL/min. Median (min, max) predicted values from compartmental analysis.

Apart from AUC<sub>0-τ</sub>, in subjects with CL<sub>Cr</sub> between 20 and 49 mL/min, the exposure measures for subjects with CL<sub>Cr</sub> < 50 mL/min are different from subjects with adequate renal function (CL<sub>Cr</sub> > 50 mL/min).

#### Comment on Simulation Results

- The accuracy of the simulation results is currently unclear, particularly if non-linearity is present. The accuracy of the simulations will be evaluated in a future PK study. However, due to the availability of just one tablet strength it is challenging to obtain more suitable regimens than those proposed by the sponsor.
- It should be noted that AUC and C<sub>max</sub> achieved in the 10 – 19 mL/min group are comparable to the AUC and C<sub>max</sub> that would be achieved with a 20 mg once daily dose. In addition, these exposures are likely to overlap the lower limit of exposure for a 30 mg once daily dose. The 30 mg dose has shown mild nephrotoxicity in a pivotal clinical trial. There is no safety information at the 20 mg dose. Additionally, the median C<sub>trough</sub> in the two CL<sub>Cr</sub> groups (CL<sub>Cr</sub> < 50 mL/min) that require dose adjustment are lower than in subjects with adequate renal function. The clinical significance of these exposure differences are yet to be determined.

#### Sponsor's Safety Summary

Oral administration of 1 or 2 doses of adefovir dipivoxil 10 mg to adult subjects with normal renal function or varying degrees of renal impairment (mild, moderate, or severe impairment or end stage renal disease) appeared to be generally safe and well tolerated. The most common adverse events included headache, asthenia, back pain, and vomiting.

#### Conclusions/Recommendations:

##### General Recommendation:

Renal function of patients receiving adefovir dipivoxil should be routinely monitored, as drug causes nephrotoxicity at high exposures (≥ 30 mg once daily). It should be noted that the nephrotoxic potential and safety profile of adefovir dipivoxil doses between 10 and 30 mg once daily is unknown.

##### Pharmacokinetic Observations

- The pharmacokinetics of adefovir following administration of adefovir dipivoxil 10 mg were not affected to an extent requiring dosage modification in subjects with CL<sub>Cr</sub> ≥ 50 mL/min.
- Subjects with calculated CL<sub>Cr</sub> < 50 mL/min or those with ESRD requiring hemodialysis have substantial reductions in the renal elimination of adefovir and higher systemic adefovir exposures requiring dose adjustment.

- A single high-flux hemodialysis session removed approximately 35 % of adefovir, and should be acceptable to facilitate adefovir administration in this subject population, provided there are no major safety concerns with long-term intermittent exposure to high adefovir levels (comparable to lower limit of 30 mg once daily adefovir dipivoxil levels).

#### Dosage Adjustment

Based on exposure data from this pharmacokinetic renal impairment study, and the limitation of only one dosage strength, the proposed dosing for patients with  $CL_{cr}$  between 10 and 50 mL/min are acceptable. A dosing recommendation can not be made for non-hemodialysis subjects with  $CL_{cr} < 10$  mL/min, because there are no exposure data in these subjects.

#### **Proposed Adefovir dipivoxil dosage**

Calculated Creatinine Clearance (mL/min)	10 mg Dosing Interval	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

#### **Appendix**

##### **Demographic Summary by Group and Overall**

Demographic Variable	Normal Renal Function (n = 8)	Renal Function Impairment				Total (n = 41)
		Mild (n = 8)	Moderate (n = 7)	Severe (n = 10)	ESRD (n = 8)	
<b>Gender</b>						
Female	2 (25 %)	5 (63 %)	4 (57 %)	1 (10 %)	0 (0 %)	12 (29 %)
Male	6 (75 %)	3 (37 %)	3 (43 %)	9 (90 %)	8 (100 %)	29 (71 %)
<b>Race</b>						
Caucasian	8 (100 %)	8 (100 %)	7 (100 %)	9 (90 %)	6 (75 %)	38 (93 %)
Black	0 (0 %)	0 (0 %)	0 (0 %)	1 (10 %)	2 (25 %)	3 (7 %)
<b>Age (years)</b>						
Mean ± SD	42.6 ± 16.0	58.6 ± 10.5	51.4 ± 13.9	53.2 ± 11.5	44.3 ± 12.2	50.1 ± 13.6
Median	45.5	63	43	55.5	47	51
Range	21 to 65	40 to 70	38 to 71	36 to 70	22 to 62	21 to 71
<b>Weight (kg)</b>						
Mean ± SD	75.8 ± 6.8	69.0 ± 8.7	68.1 ± 13.1	71.7 ± 10.7	76.6 ± 21.7	72.3 ± 12.9
Median	79.4	70.3	71.0	73.5	73.9	74.5
Range	63 to 81	53 to 78	50 to 81	56 to 93	46 to 118	46 to 118
<b>Height (cm)</b>						
Mean ± SD	174.5 ± 7.8	167.0 ± 8.3	168.2 ± 11.0	171.1 ± 7.1	174.0 ± 10.2	171.0 ± 8.9
Median	176.5	168.0	169.0	170.5	174.5	171.0
Range	163 to 186	154 to 178	155 to 182	161 to 181	158 to 187	154 to 187

Study Title: A Phase 1, Open-Label, Parallel-Group, Single Dose Study to Evaluate the Pharmacokinetics of Adefovir Dipivoxil in Subjects with Normal and Impaired Hepatic Function

Study No.: GS-00-474

Principal Investigators/Study Centers:

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### **Background and Study Rationale**

Adefovir dipivoxil 10 mg will be used in patients with varying degrees of hepatic impairment due to advanced chronic HBV infection. Therefore, it is prudent to investigate the potential differences in the pharmacokinetics and safety of adefovir dipivoxil 10 mg in this population. Ultimately the information obtained in this study can be used to establish dosing guidelines for adefovir dipivoxil use in patients with hepatic impairment. It is noted that ADV is excreted principally unchanged by the kidneys therefore one does not expect hepatic impairment to have a significant effect on adefovir PK. However, persistent hepatitis B viral replication in chronically infected patients often results in liver damage and dysfunction, which may lead to pathologies in multiple organ systems. It is well known that changes in blood flow through the liver may alter the disposition of some drugs. In particular, altered hepatic and splanchnic blood flow, and fluid volume related to portal hypertension may lead to alterations in renal blood flow and development of renal impairment in advanced liver disease.

### **Objectives:**

- To evaluate the pharmacokinetics of adefovir following administration of a single dose of adefovir dipivoxil 10 mg in subjects with normal and varying degrees of hepatic impairment.
- To develop dosing guidelines for subjects with impaired hepatic function.
- To evaluate the safety of adefovir dipivoxil 10 mg in subjects with normal and varying degrees of hepatic impairment.

### **Study Design:**

This was a Phase 1, open-label, single dose pharmacokinetic (PK) study. There were three treatment groups. Subjects in each group received a single 10 mg dose of adefovir dipivoxil.

Group (1) healthy subjects with normal hepatic function, Child Pugh Class A

Group (2) subjects with moderate hepatic impairment, Child Pugh Class B

Group (3) subjects with severe hepatic impairment, Child Pugh Class C

The severity of hepatic impairment was assessed using the Child-Pugh classification system (see appendix). Subjects with normal hepatic function were used as the control group. Subjects received drug while fasting.

### **Study Subjects**

Twenty-four evaluable subjects total; 3 groups with 8 subjects in each group. Healthy subjects with normal hepatic function and subjects with moderate or severe hepatic impairment caused by non-hepatitis B induced liver cirrhosis.

### ***Demographic and Other Baseline Characteristics***

All 24 subjects enrolled in the study were Caucasian, with the majority of subjects being male. The weights and heights of subjects were comparable across all three groups. However, subjects with normal hepatic function were notably younger (median 22 years, range 19 to 51 vs. median  $\approx$  50 and range 44 to 66 years in subjects with impaired hepatic function) Additionally, subjects in Group 1 were predominantly female. The imbalance with respect to age and gender are contrary to the recommendations in the *Draft Guidance for Industry: Hepatic Impairment Studies*. Demographic

characteristics are summarized in Table II of appendix. However, these deviation from the guidance's recommendation is acceptable because it is difficult to enroll subjects in hepatic impairment studies. The protocol deviations listed below further highlight the difficulty in conducting these studies.

**Protocol Deviations**

It is noted that ten subjects with hepatic impairment (4 with moderate impairment and 6 with severe impairment) did not meet the inclusion and exclusion criteria for this protocol. However these subjects were granted exemptions to specific entry criteria including low platelet count, elevated bilirubin, decreased serum phosphorus, and low hemoglobin. The sponsor indicates that these protocol exemptions were not clinically significant. Three subjects were also on concomitant medications before ADV DP treatment started (see Appendix: Concomitant Medications)

**Test Product and Batch No.**

Adefovir Dipivoxil 10 mg tablet: Manufactured by Gilead Sciences, Inc. Lot No. D906A1

**Sample Collection**

- Blood samples for PK analysis were collected at the following time points: 0/predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours.
- Urine samples for pharmacokinetic analysis were collected during the following time intervals: 0/predose void, 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hours.

**Safety Evaluation**

Safety was evaluated by collecting laboratory samples at baseline and at specified times during the study, and by monitoring adverse events throughout the study.

**Pharmacokinetic Analyses**

The following ADV PK measures were determined:  $C_{max}$ ,  $T_{max}$ ,  $C_{last}$ ,  $T_{last}$ ,  $k_{el}$ ,  $T_{1/2z}$ ,  $AUC_{0-1}$ ,  $AUC_{0-\infty}$ ,  $V_z/F$ ,  $CL/F$  and  $CL_{Cr}$ . Exposure measures obtained in Groups 2 and 3 were compared to Group 1 exposures using standard PK-statistical procedures.

**Assay**

A validated \_\_\_\_\_ bioanalytical method was used to analyze samples for ADV content. The assay was performed at \_\_\_\_\_

The method was acceptable and had the following characteristics.

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

**Pharmacokinetic Results and Discussion**

All subjects were included in all analyses, except 2 subjects in the group with moderate hepatic impairment. These two subjects were excluded from the summary pharmacokinetics.

Pharmacokinetic parameters for ADV are summarized in Table I. The pharmacokinetics of adefovir observed in this study were similar to those observed in previous studies of healthy subjects (Protocols GS-00-475 and GS-00-476) and patients with chronic HBV infection (Protocol GS-00-472). However, PK data in this study were more variable than in other studies.

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

	AUC <sub>0-1</sub> (ng•hr/mL)	AUC <sub>0-∞</sub> (ng•hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2z</sub> (hr)	V <sub>d</sub> /F (mL/kg)
<b>Normal Hepatic Function (N = 8); Mean ± SD CL<sub>cr</sub> = 121 ± 28 mL/min</b>						
Gmean (95 % CI)	185 (154 - 223)	198 (166 - 236)	18 (15 - 23)		6.3 ± 0.6 <sup>^</sup>	
Minimum						
Median	175.79	187.27	16.81	1.25	6.17	3773.11
Maximum						
<b>Moderate Hepatic Impairment (N = 6); Mean ± SD CL<sub>cr</sub> = 99 ± 41*</b>						
Gmean (95 % CI)	219 (104 - 459)	250 (130 - 481)	16 (9 - 27)		10.8 ± 4.3*	
Minimum						
Median	211.57	237.17	16.31	2.25	9.78	5769.95
Maximum						
<b>Severe Hepatic Impairment (N = 8); Mean ± SD CL<sub>cr</sub> = 107 ± 37</b>						
Gmean (95 % CI)	190 (123 - 293)	213 (145 - 314)	14 (11 - 18)		10.4 ± 1.7	
Minimum						
Median	232.74	251.66	16.67	1.50	10.79	5686.42
Maximum						

NA = Not applicable

\*Subjects 0592-1003 and 0592-1009 had extrapolated % AUC<sub>0-∞</sub> greater than 30 % and therefore, in accordance with the protocol, were not included in the summary statistics.

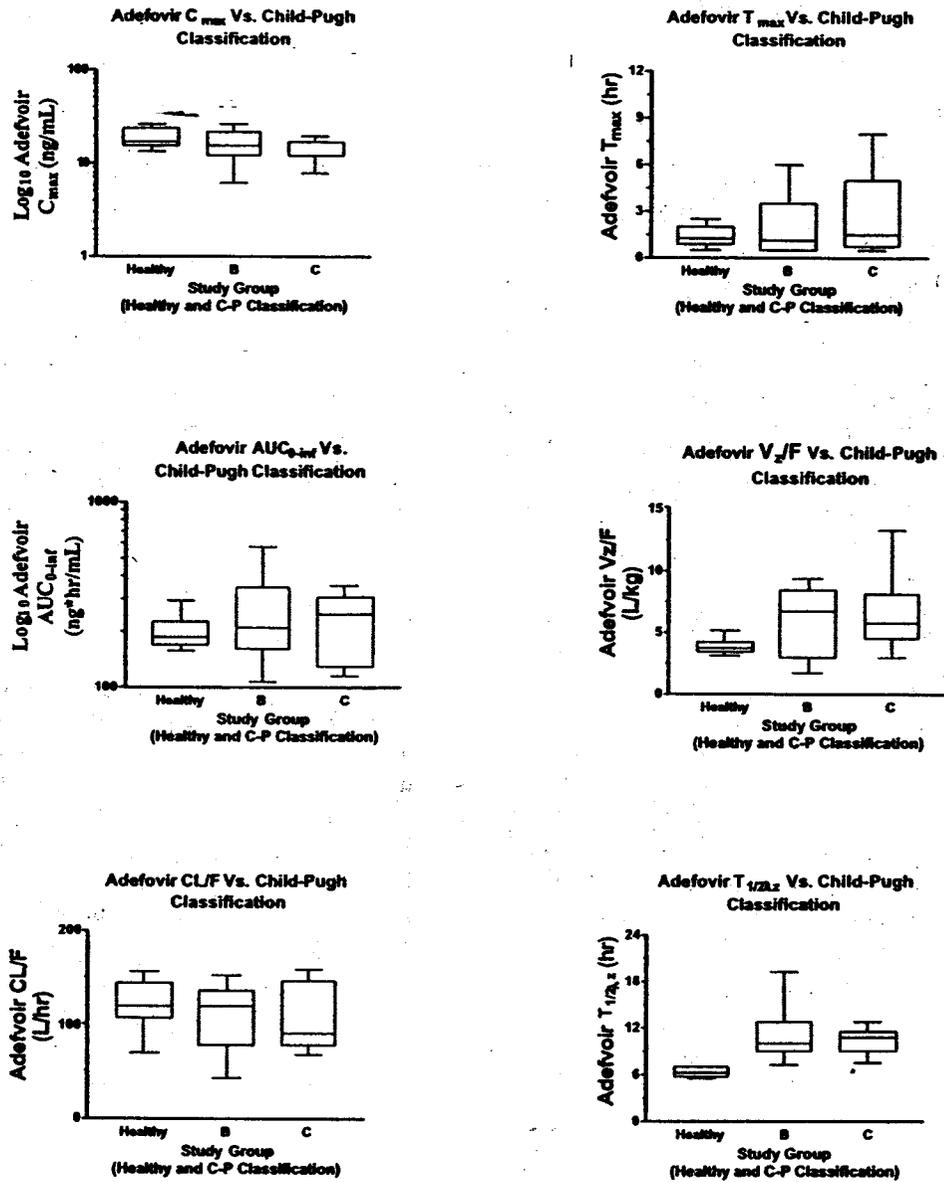
\* If two subjects with CL<sub>cr</sub> < 2 are excluded, the mean ± CL<sub>cr</sub> = 124 ± 16 mL/min and half-life = 11.6 ± 5.3 hr

<sup>^</sup> arithmetic mean ± SD

Following oral administration of adefovir dipivoxil 10 mg in the fasted state, ADV appeared to be absorbed relatively rapidly in all Groups, however, the time required for absorption (achieve T<sub>max</sub>) appeared to increase with increasing severity of hepatic impairment. Similarly the terminal half-life appeared to increase with increasing severity of hepatic impairment, even though ADV is not hepatically cleared. It is not known if the t<sub>1/2</sub> differences would be more pronounced upon multiple dosing. PK measures for Group 2 were more variable than in other groups; this increased variability may be due partially to the smaller number of subjects in Group 2 (n = 6) compared to other groups (n = 8). Also, it is noted that two subjects in the moderate hepatic impairment group (0592-1002 and 0592-1007) had increased ADV exposures (AUC<sub>0-∞</sub> 569 and 447 ng•hr/mL) relative to other subjects in Group 2. The exposure increases were consistent with their mild to moderate renal impairment (creatinine clearance by Cockcroft-Gault method 51.59 and 43.82 mL/min, respectively). The mean CL<sub>cr</sub> was 121, 108 (all subjects), and 107 mL/min for Groups 1, 2 and 3, respectively. The mean CL<sub>cr</sub> for group two increased by 20 mL/min, from 120 to 128 mL/min when subjects with impaired renal function were excluded in the analysis.

The sponsor plotted ADV PK parameters in relation to the degree of hepatic impairment to explore the effect of hepatic impairment on adefovir exposure and PK measures (figure 1). The plots highlight the findings previously mentioned. In brief, the plots indicate that despite increased variability in groups 2 and 3, most ADV PK measures were not significantly altered in subjects with moderate or severe hepatic impairment relative to healthy subjects. In general, there was substantial overlap in ADV PK parameters in all three groups. According to the sponsor, these data are consistent with the literature indicating that marked alterations in drug exposure are often not observed in patients with chronic hepatitis until the setting of end stage cirrhotic disease. The sponsor's assertion appears reasonable because data obtained in this study are comparable to previous ADV PK data in subjects with intact hepatic function. Based on the single-dose data it does not appear that the proposed 10 mg once daily dose of adefovir dipivoxil needs to be modified in subjects with hepatic impairment.

**Figure 1: Adefovir Pharmacokinetics and Degree of Hepatic Impairment**



Figures represent minimum, 25<sup>th</sup> percentile, median, 75<sup>th</sup> percentile, and maximum for each group.

### Exposure Comparisons

The sponsor calculated 90 % confidence intervals (CI) for AUC and  $C_{max}$  around the ratio of geometric means between each of the hepatic impairment groups and healthy subjects (Table II).

Table II: Effect of Hepatic Impairment on Relative Adefovir Exposure

	Moderate*/Healthy		Severe/Healthy	
	GMR (%)	90 % CI	GMR (%)	90 % CI
AUC <sub>0-∞</sub>	126.28	79.73 - 200.01	107.77	78.96 - 147.10
C <sub>max</sub>	86.44	58.34 - 128.08	78.46	61.85 - 99.52

#### \* Comment on Confidence Interval

The geometric mean AUC and resulting geometric mean ratio was significantly affected by two subjects with impaired renal function. If data from all subjects ( $n = 6$ ) were included the geometric mean AUC is 219 ng hr/mL and if the two subjects with renal impairment were excluded ( $n = 4$ ) the mean geometric mean AUC is 148 ng hr/mL. The resulting geometric mean ratio when the two subjects are excluded is 80 % and the associated 90 % CI will be narrower (not calculated). The narrowing of the confidence interval provides indirect evidence that the variability in the GMR is due primarily to the two subjects with both impaired renal and hepatic function

Based on geometric mean ratios and associated 90 % CIs for ADV  $C_{max}$ , the mean  $C_{max}$  for subjects in Group 2 was comparable to the mean  $C_{max}$  in healthy subjects. On the other hand, the mean  $C_{max}$  for Group 2 subjects was slightly lower than the mean  $C_{max}$  in Group 1. Geometric mean ADV AUC<sub>0-∞</sub>s were similar in subjects with moderate hepatic impairment (GMR = 126 %) or severe impairment (GMR = 108 %) relative to the AUCs observed in healthy subjects. It is noted that the calculated CIs are fairly wide which may be reflective of variability due to small sample size, inclusion of data from subjects with impaired renal function (Group 2) and other physiological factors (e.g. alterations in fluid homeostasis in subjects) associated with impaired hepatic function. It is noted that protein binding is not expected to have a significant on ADV clearance or exposure because protein binding is insignificant (protein binding < 5 %).

#### Safety observations (Sponsor's summary):

Two subjects with normal hepatic function experienced one adverse event each (mild dry mouth, moderate headache). The investigator considered both of the events to be related to study treatment. No other adverse events were reported. No deaths or other serious adverse events occurred during the study.

#### Pharmacokinetic Conclusions and Recommendations

##### 1. Dosing in Hepatic Impairment

The alterations in adefovir pharmacokinetics in subjects with moderate (Child-Pugh Classification B) or severe (Child-Pugh Classification C) hepatic impairment relative to healthy subjects do not appear sufficient enough to warrant alterations in dose or dosing frequency of adefovir-dipivoxil. Consequently, adefovir dipivoxil may be dosed as 10 mg once daily in patients without regard to hepatic function.

##### 2. Dosing in subjects with both impaired hepatic and renal function

The sponsor should evaluate the simultaneous effect of hepatic and renal impairment on adefovir pharmacokinetics. It is likely that patients with both of these conditions or similar conditions will be candidates for adefovir treatment, and the proposed dosage may be inappropriate. A multiple-dose study design will be desirable to confirm that ADV PK maintain time-independence in the setting of simultaneous hepatic and renal impairment.

**Comment**

The sponsor has indicated that a PK study in HBV-infected subjects with both impaired renal and hepatic function will be conducted (Study 526).

**Safety Conclusions**

Administration of a single oral dose of adefovir dipivoxil 10 mg appeared to be safe and generally well tolerated in these healthy adult subjects and adult subjects with moderate and severe hepatic impairment.

**Appendix**

**Child-Pugh Score**

Child-Pugh Score	Child-Pugh Class	Hepatic Status
7-9	B	Moderate Impairment
>9	C	Severe Impairment

**Demographic Summary by Group and Overall**

Demographic Variable	Normal (N = 8)	Moderate Impairment (N = 8)	Severe Impairment (N = 8)	All (N = 24)
<b>Gender</b>				
Female	6 (75 %)	2 (25 %)	1 (12.5 %)	9 (37.5 %)
Male	2 (25 %)	6 (75 %)	7 (87.5 %)	15 (62.5 %)
<b>Race</b>				
Caucasian	8 (100 %)	8 (100 %)	8 (100 %)	24 (100 %)
<b>Age (yr.)</b>				
Mean ± SD	29.0 ± 12.82	52.1 ± 8.56	55.1 ± 7.38	45.4 ± 15.20
Median	22.0	49.0	55.0	48.0
Min - Max	19 to 51	44 to 68	45 to 66	19 to 68
<b>Weight (kg)</b>				
Mean ± SD	65.5 ± 8.41	75.0 ± 10.56	63.9 ± 11.00	68.2 ± 10.83
Median	66.4	74.5	62.5	66.5
Min - Max	50.4 to 77.8	62 to 93.5	51.1 to 87.3	50.4 to 93.5
<b>Height (cm)</b>				
Mean ± SD	167.4 ± 9.33	168.9 ± 9.79	168.0 ± 7.23	168.1 ± 8.48
Median	164.5	172.5	169.5	171.0
Min - Max	158 to 183	147 to 178	155 to 175	147 to 183

**Concomitant Medications**

Three subjects were receiving concomitant medications before entering the study for reasons not recorded in the medical history. Subject 0592-1004 was taking a benzamide (tiapride) for encephalopathy and a benzodiazepam related drug (zopiclone) for insomnia. Subject 0592-1008 was taking zopiclone for insomnia and subject 0592-2002 was taking diazepam for insomnia. None of these drugs are expected to alter ADV PK.

Study Title: A Phase I, Randomized, Open-Label, Multiple-Dose, Drug Interaction Study to Evaluate the Pharmacokinetics of Adefovir Dipivoxil, Lamivudine, Ibuprofen, Acetaminophen and Trimethoprim/Sulfamethoxazole in Healthy Volunteers  
Study No.: GS-00-475  
Investigators:  
Study Centers:  
Study Period: January 30, 2001 (First Patient Enrolled)  
April 28, 2001 (Last Patient Observation)

### Background and Study Rationale

*In vitro* studies have shown that adefovir is not a substrate or inhibitor of the CYP450 isozyme system; thus, it is unlikely that adefovir would interact with drugs metabolized by the liver through this system. Following adefovir dipivoxil administration, adefovir is eliminated by the kidney with renal clearance of adefovir exceeding glomerular filtration rate, indicating a component of active tubular secretion. 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** - possibility of coadministration of these agents in HIV/HBV co-infected patients or in the event that patients receive these drugs as combination therapy for HBV infection.
- **Ibuprofen** - selected because it is/was frequently coadministered in the database of controlled clinical trials of adefovir dipivoxil for chronic HBV infection (based on database query). Additionally, both ibuprofen and adefovir exhibit renal toxicity
- **Acetaminophen** - selected because it is/was frequently coadministered in the database of controlled clinical trials of adefovir dipivoxil for chronic HBV infection (based on database query). Additionally, acetaminophen is hepatotoxic and may affect hepatic function of HBV infected patients.
- **Trimethoprim/sulfamethoxazole** 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

### Objectives

- To evaluate the pharmacokinetics of adefovir dipivoxil, lamivudine, ibuprofen, acetaminophen, and trimethoprim/sulfamethoxazole when administered alone.
- To evaluate the pharmacokinetics of adefovir dipivoxil when co-administered with lamivudine, ibuprofen, acetaminophen, and trimethoprim/sulfamethoxazole.
- To evaluate the pharmacokinetics of lamivudine, ibuprofen, acetaminophen, and trimethoprim/sulfamethoxazole when co-administered with adefovir dipivoxil.
- To evaluate the safety of adefovir dipivoxil 10 mg.

### Study Design:

This was a Phase I, randomized, open-label, multiple-dose, crossover, drug interaction study.

There were 4 cohorts with 18 evaluable subjects in each cohort. The cohorts were as follows:

Cohort 1: adefovir dipivoxil (10 mg) and lamivudine

Cohort 2: adefovir dipivoxil (10 mg) and ibuprofen

Cohort 3: adefovir dipivoxil (10 mg) and acetaminophen

Cohort 4: adefovir dipivoxil (10 mg) and trimethoprim/sulfamethoxazole

Each cohort consisted of 3 treatment periods that were arranged in 6 sequences as follows: ACB, BAC, CBA, BCA, CAB, ABC. There was a 7-day washout period between treatments for all cohorts.

A: adefovir dipivoxil 10 mg administered once daily for 7 days.

B: combination treatment (adefovir + coadministered drug) given at specified interval for specified number of days

C: coadministered drug alone for specified number of days to reach steady state

**Duration of Treatment (Single Agent):**

Adefovir dipivoxil (ADV DP): once daily for 7 days

Lamivudine (3TC): once daily for 7 days

Ibuprofen (IBF): 3 times daily for 2 days + a single dose on 3<sup>rd</sup> dayAcetaminophen (ACN): 4 times daily for 2 days + single dose on 3<sup>rd</sup> dayTrimethoprim/sulfamethoxazole (TMP/SMX): twice daily for 3 days + a single dose on 4<sup>th</sup> day**Dose Selection Rationale**

Adefovir dipivoxil 10 mg was selected for this study because it is the proposed clinical dose for HBV treatment. The lamivudine dose of 100 mg is the approved dose for the treatment of HBV infection. Acetaminophen 1000 mg, ibuprofen 800 mg, and trimethoprim 160 mg/sulfamethoxazole 800 mg are the highest recommended clinical doses and were selected for this study to maximize the interaction potential with adefovir dipivoxil. All drugs were dosed to achieve steady state concentrations.

**Subjects**

A total of 81 healthy volunteers, 41 males and 40 females, were enrolled in the study, and 71 subjects, 36 males and 35 females, completed the study. All 81 subjects were included in the safety analysis. There were 75 subjects included in the statistical analysis of pharmacokinetics.

Demographic and Other Baseline Characteristics are summarized in Table I.

A demographic summary of the subjects by cohort and overall is provided in Table I.

Table I: Demographic Summary by Cohort and Overall

Demographic Variable	Lamivudine (Cohort 1) (N = 20)	Ibuprofen (Cohort 2) (N = 21)	Acetaminophen (Cohort 3) (N = 20)	TMP/SMX (Cohort 4) (N = 20)
<b>Gender</b>				
Female	10	10	10	10
Male	10	11	10	10
<b>Ethnicity</b>				
Asian	0	0	2	0
Black	4	2	2	2
Caucasian	12	16	14	17
European/MidEast	0	1	0	0
Hispanic	4	2	2	1
Age, Mean ± SD (yr.)	33 ± 9	33 ± 8	31 ± 10	29 ± 9
Weight, Mean ± SD (kg)	68.2 ± 10.9	72.1 ± 13.0	71.9 ± 13.0	73.9 ± 14.1
Height, Mean ± SD (cm)	173 ± 9	173 ± 10	173 ± 7	174 ± 10

**Patient Disposition and Protocol Deviations**

Seventy-one subjects completed the study. Four subjects discontinued due to adverse events (#16, #32, #65, and #77), 2 subjects withdrew consent (#62 and #73), 1 subject was lost to follow-up (#10), 1 subject did not check-in (#29). Minor protocol deviations occurred in the study, but these deviations do not appear to impact the PK study results.

**Test Products and Lot Number:**

- Adefovir Dipivoxil, Gilead Sciences 10 mg tablets, Lot No. D906A1
- Eпивir-HBV® (lamivudine) 100 mg tablets, Glaxo Wellcome Inc. Lot No. OK507
- Motrin® (ibuprofen), 800 mg tablets, Pharmacia & Upjohn Company, Lot No. 66CST
- Extra Strength Tylenol® (acetaminophen), 1000 mg caplets, McNeil Consumer Healthcare, Lot No. DMM131

- Bactrim™ DS (trimethoprim 160 mg/sulfamethoxazole 800 mg) tablets, Roche Laboratories, Inc., Lot No. 1335

#### Pharmacokinetic Analyses

The following pharmacokinetic parameters were evaluated for all drugs:  $AUC_{0-\tau}$ ,  $C_{max}$ ,  $C_{min}$ ,  $C_{last}$ ,  $T_{max}$ ,  $T_{min}$ ,  $T_{last}$ ,  $T_{1/2\lambda z}$ ,  $V_z/F$ ,  $CL/F$ ,  $CL_{renal}$ , and % dose recovered.

#### Statistical Analyses

Drug-drug interactions were evaluated using standard PK-statistical analyses recommended in *Guidance for Industry* on drug-drug interactions.

#### Safety Analyses

Safety was evaluated by collection of laboratory samples (both plasma and urine) at baseline and at various time points during the study, and by collection of adverse events throughout the duration of the study.

#### Assay

Adefovir Concentrations of adefovir in human plasma samples were determined using a validated bioanalytical method. The method was validated by \_\_\_\_\_ and had the following characteristics:

##### *Adefovir*

Linear Range: \_\_\_\_\_

Lower limit of quantitation (LLOQ): \_\_\_\_\_

Sensitivity/specificity to adefovir: high degree; lamivudine, ibuprofen, acetaminophen, trimethoprim, or sulfamethoxazole did not interfere with the adefovir assay. In addition, ibuprofen did not interfere with adefovir in the urine method.

Concentrations of lamivudine, ibuprofen, acetaminophen, trimethoprim, and sulfamethoxazole in human plasma samples were determined by validated \_\_\_\_\_ with UV detection bioanalytical methods. \_\_\_\_\_ validated the assay for all coadministered drugs with the exception of TMP/SMX that was validated by \_\_\_\_\_. Adefovir did not interfere with the determination of any of the coadministered compounds. The characteristics of the bioanalytical methods for each of the compounds is summarized below:

##### *Coadministered Drugs*

###### Lamivudine

Linearity range: \_\_\_\_\_

LLOQ: \_\_\_\_\_

Highly sensitive and specific to lamivudine.

###### Ibuprofen

Linearity range: \_\_\_\_\_

LLOQ: \_\_\_\_\_

Highly sensitive and specific to ibuprofen

###### Acetaminophen

Linearity range: \_\_\_\_\_

LLOQ: \_\_\_\_\_

Highly sensitive and specific to acetaminophen.

### Trimethoprim and sulfamethoxazole

Linearity range for trimethoprim: \_\_\_\_\_

Linearity range for sulfamethoxazole: \_\_\_\_\_

LLOQ for trimethoprim and sulfamethoxazole were \_\_\_\_\_ respectively. The method was highly sensitive and specific to trimethoprim and sulfamethoxazole

### Specimen collection

Specimens were collected on specified days after treatment administration.

Blood samples: 0/predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 hours.

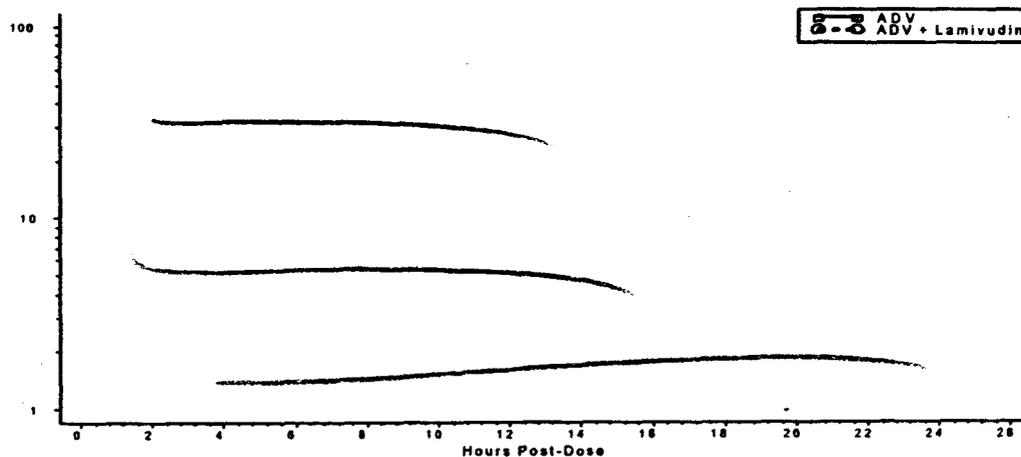
Urine samples: 0/predose void, 0-4, 4-8, 8-12, 12-24 hours.

### Results

#### ADV – 3TC Drug-drug Interaction (Cohort 1)

The plasma concentration-time (PC-T) profiles of ADV following administration of ADV DP alone and in combination with lamivudine resulted in similar adefovir PC-T profiles (figure 1). Administration of lamivudine alone and in combination with adefovir dipivoxil resulted in similar lamivudine PC-T profiles (figure 2).

Figure 1: Adefovir Plasma Concentration vs. Time Plot (ADV-3TC study)



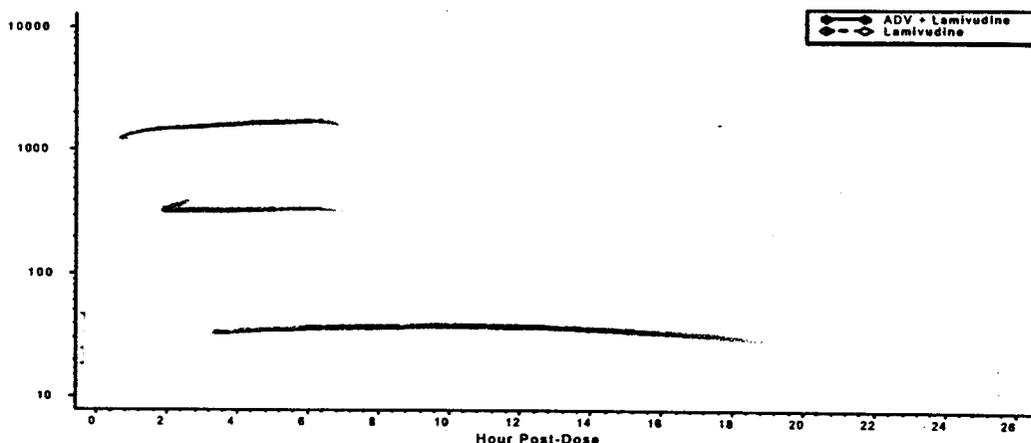
ADV PK parameters and applicable statistical comparisons obtained in the ADV-3TC drug interaction study are summarized below

#### Plasma Adefovir Pharmacokinetic Parameters (n = 17) Alone and with Lamivudine

	ADV DP 10 mg	ADV DP 10 mg + 3TC 100 mg	% GMR (ADV DP + Lamivudine/ ADV DP Alone)
Geometric Mean $C_{max}$ (ng/mL)	21.14	21.07	99.7 % (91.4 % - 108.8 %)
Geometric Mean AUC $_{(0-t)}$ (ng•hr/mL)	197.59	196.08	99.2 % (92.5 % - 106.5 %)
Median $T_{max}$ (hr)	1.00	0.80	-
Median $T_{1/2\lambda_z}$ (hr)	7.17	7.24	-

For both AUC and  $C_{max}$  the ratio of geometric least squares means for ADV when ADV-DP was dosed in combination with lamivudine versus adefovir dipivoxil alone were approximately equal to 100 %, and the 90 % CI were between 90 and 110 %. Based on these results, 3TC did not affect the PK of ADV.

Figure 2: Lamivudine Plasma Concentration vs. Time Plot (ADV-3TC study)



Lamivudine PK parameters and applicable statistical comparisons obtained in this drug-drug interaction study are summarized below.

**Plasma Lamivudine Pharmacokinetic Parameters Alone and with Adefovir Dipivoxil (n = 18)**

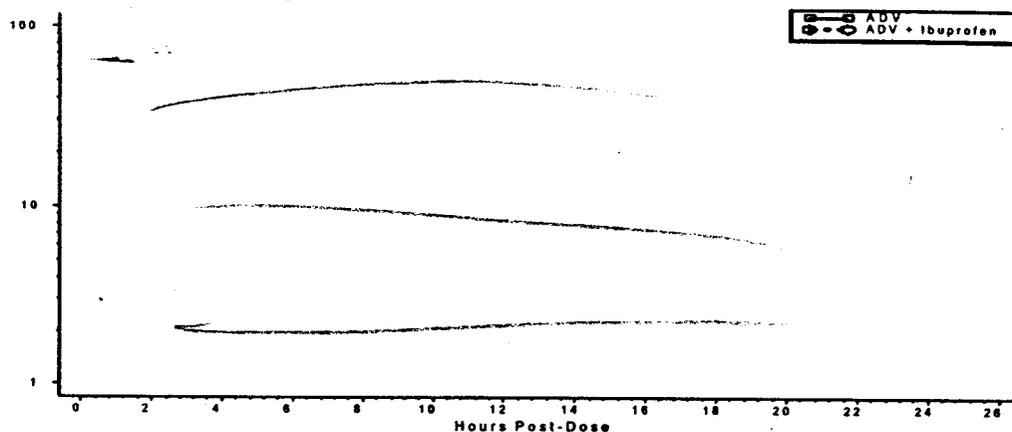
	Lamivudine 100 mg Alone	Lamivudine 100 mg + ADV DP 10 mg	% GMR for 3TC + ADV DP/3TC (90 % CI)
Geometric Mean $C_{max}$ (ng/mL)	998.6	996.9	99.8 % (89.5 % - 111.3 %)
Geometric Mean AUC <sub>(0-∞)</sub> (ng•hr/mL)	4499.8	4499.1	100.0 % (95.6 % - 104.6 %)
Median $T_{max}$ (hr)	1.0	1.0	-
Median $T_{1/2\lambda_z}$ (hr)	9.7	9.4	-

For both AUC and  $C_{max}$ , the ratio of geometric least squares means for 3TC when adefovir dipivoxil was dosed in combination with lamivudine versus 3TC alone were approximately equal to 100 % and the 90 % CIs were between 89 and 112 %. Based on these results, ADV did not affect the PK of 3TC.

**ADV – IBF Drug-drug Interaction (Cohort 2)**

ADV concentrations following administration of ADV-DP with ibuprofen (IBF) were higher than ADV concentrations obtained when ADV-DP was administered alone (figure 3). IBF concentrations were similar after administration of IBF alone and in combination with ADV-DP (figure 4).

Figure 3: Adefovir Plasma Concentration vs. Time Plot (ADV-IBF study)

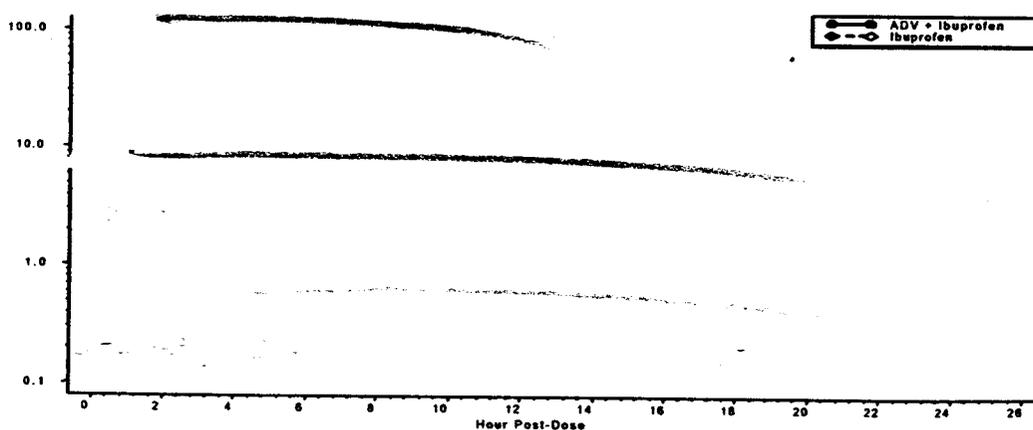


ADV PK parameters and applicable statistical comparisons obtained in the ADV-IBF drug interaction study are summarized in the table below.

Table Plasma Adefovir Pharmacokinetic Parameters Alone and with Ibuprofen (n = 18)

	ADV DP 10 mg Alone	ADV DP 10 mg + ibuprofen (IBF) 800 mg	% GMR for ADV+IBF/ADV (90 % CI)
Geometric Mean $C_{max}$ (ng/mL)	20.77	27.54	132.6 % (120.6 % - 145.7 %)
Geometric Mean $AUC_{(0-t)}$ (ng•hr/mL)	204.34	250.72	122.7% (112.9 % - 133.4 %)
Median $T_{max}$ (hr)	3.00	3.02	-
Median $T_{1/2\lambda_z}$ (hr)	6.67	6.53	-

Figure 4: Ibuprofen Plasma Concentration vs. Time Plot (ADV-IBF study)



The ratio of geometric least squares means for adefovir AUC and  $C_{max}$  when adefovir dipivoxil was dosed in combination with ibuprofen versus adefovir dipivoxil alone were above 120 % and the CIs fell outside 80 – 125 %. Based on these findings IBF affects the exposure of ADV.

### Urinary Adefovir Pharmacokinetic Parameters

The following ADV PK parameters in urine were obtained in the IBF-ADV drug-drug interaction study.

#### Urine Adefovir Pharmacokinetic Parameters Alone and with Ibuprofen

	ADV 10 mg alone (n = 18)	ADV 10 mg + Ibuprofen 800 mg (n = 18)
Median % Dose Recovered	45.31	55.31
Median $CL_{renal}$ (mL/hr/kg)	175.82	169.00
Median ADV Urinary Excretion (mg)	2.47	3.02

The median adefovir urinary recovery at steady state was higher when adefovir dipivoxil was administered in combination (55 %) with ibuprofen versus alone (45 %) [ $p < 0.05$ , Wilcoxon Signed-Rank]. There were no alterations ( $p = 0.1361$ , Wilcoxon Signed-Rank) in the urinary adefovir clearance when adefovir dipivoxil was dosed concomitantly with ibuprofen versus alone.

Ibuprofen PK parameters and their applicable statistical comparisons obtained in this study are summarized in the table below.

#### Plasma Ibuprofen Pharmacokinetic Parameters Alone and with Adefovir Dipivoxil (n = 18)

	Ibuprofen 800 mg Alone	Ibuprofen 800 mg + ADV DP 10 mg	% GMR Ibuprofen + ADV DP/ Ibuprofen (90 % CI)
Geometric Mean $C_{max}$ (ng/mL)	46.932	46.831	99.8 % (90.6 % - 109.9 %)
Geometric Mean $AUC_{(0-\tau)}$ (ng•hr/mL)	177.300	168.150	94.8 % (85.7 % - 104.9 %)
Median $T_{max}$ (hr)	2.260	2.025	-
Median $T_{1/2\lambda_z}$ (hr)	2.070	1.770	-

The ratio of geometric least squares means for ibuprofen when dosed in combination with adefovir dipivoxil versus alone were 99.8 % and 94.8 % for  $C_{max}$  and  $AUC_{0-\tau}$ , respectively. The associated 90 % confidence intervals around GMR for  $C_{max}$  and  $AUC_{0-\tau}$  were between 85 and 110 %, indicating that IBF exposure was not affected by ADV.

#### Discussion of Results for Cohort 2

Based on GMR and associated 90 % CI, the administration of IBF in combination with ADV-DP had a statistically significant effect on the PK of ADV. The lower bounds of the 90 % CIs for geometric means for  $C_{max}$  and  $AUC_{0-\tau}$  were above 100 % and the upper bounds of the confidence intervals also extended above the upper limit of the equivalence (lack of effect) range (125 %). Overall these data indicate a statistically significant increase in the exposure of adefovir when adefovir dipivoxil is coadministered with ibuprofen. ADV  $C_{max}$  and  $AUC_{0-\tau}$  increased approximately 33 % and 23 %, respectively, when ibuprofen was administered with ADV DP. Despite the increased ADV exposure and increased urinary recovery, the ADV  $t_{1/2}$  and  $CL_R$  were unchanged. This suggests that ADV bioavailability, rather than clearance may be affected by coadministration with IBF. It is noted that the observed increased exposure were obtained with the highest recommended clinical dose of ibuprofen. It is unclear if the increase in ADV exposure is of a sufficient magnitude to warrant a change in adefovir dipivoxil or ibuprofen dosing. On the other hand, ADV did not alter IBF PK. Caution should be exercised ADV is coadministered with any nephrotoxic agent, and an alternative non-nephrotoxic agent should be used if necessary.

### Adefovir Dipivoxil + ACN (Cohort 3)

The plasma concentration-time profiles of ADV (figure 5) and acetaminophen (ACN) [figure 6], were unchanged when each drug was administered alone or when the drugs were coadministered

Figure 5: Adefovir Plasma Concentration vs. Time Plot (ADV-ACN study)

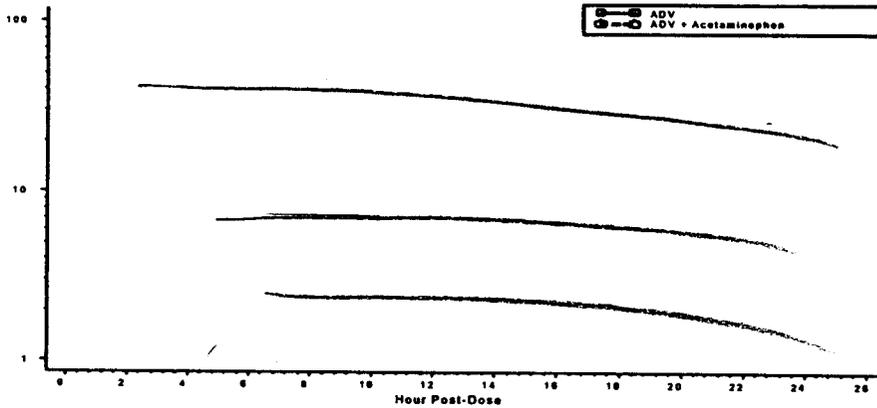
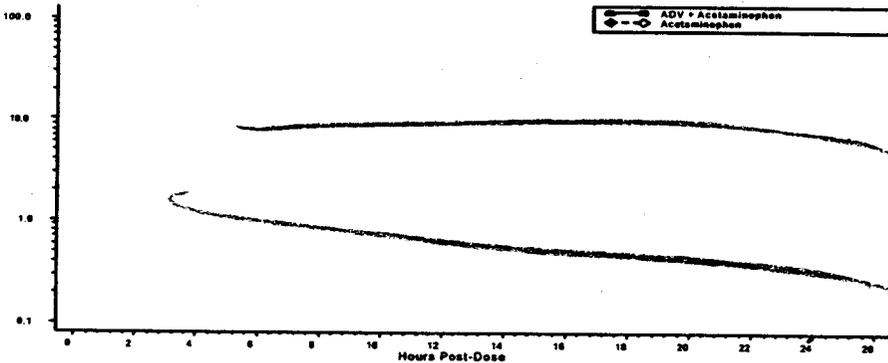


Figure 6: Acetaminophen Plasma Concentration vs. Time Plot (ADV-ACN study)



ADV PK parameters and their statistical comparisons following administration of ADV DP obtained in the acetaminophen (ACN)-ADV drug interaction study are presented below.

#### Plasma Adefovir Pharmacokinetic Parameters Alone and with Acetaminophen (n = 20)

	ADV DP 10 mg Alone	ADV DP 10 mg + Acetaminophen 1000 mg	% GMR for ADV DP + CAN/ ADV (90 % CI)
Geometric Mean $C_{max}$ (ng/mL)	23.33	26.01	111.5 % (103.1 % - 120.6 %)
Geometric Mean $AUC_{(0-\tau)}$ (ng•hr/mL)	215.00	231.37	107.6 % (103.5 % - 111.9 %)
Median $T_{max}$ (hr)	0.81	0.76	-

The ratio of geometric least squares means for adefovir when adefovir dipivoxil was dosed in combination with acetaminophen versus adefovir dipivoxil alone were approximately 110 % for  $C_{max}$  and  $AUC_{0-\tau}$ . The associated 90 % confidence intervals around the ratio of geometric means for  $C_{max}$  and  $AUC_{0-\tau}$  were between 103 and 112 %, indicating a lack of drug interaction.

ACN PK parameters and applicable statistical comparisons obtained in this study are summarized below:

**Plasma Acetaminophen (ACN) Pharmacokinetic Parameters Alone and with Adefovir Dipivoxil (n = 20)**

	ACN 1000 mg Alone	ACN 1000 mg + ADV DP 10 mg	% GMR ACN + ADV DP/ ACN (90 % CI)
Geometric Mean $C_{max}$ ( $\mu\text{g/mL}$ )	16.184	16.469	101.8 % (93.0 % - 111.4 %)
Geometric Mean $AUC_{(0-\tau)}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	48.809	49.369	101.2 % (95.6 % - 107.0 %)
Median $T_{max}$ (hr)	0.560	0.755	-

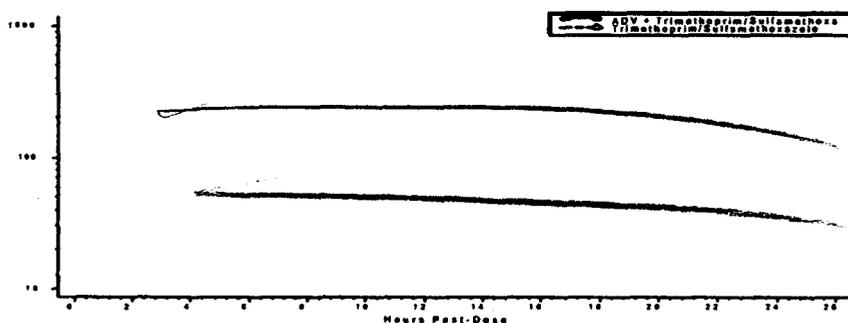
The ratio of geometric means for acetaminophen when dosed in combination with adefovir dipivoxil versus alone were approximately 100 % for  $C_{max}$  and  $AUC_{0-\tau}$ . The 90 % confidence intervals around the ratio of geometric means for  $C_{max}$  and  $AUC_{0-\tau}$  were 93.0 %-111.4 % and 95.6 %-107.0 %, respectively. These findings indicate that ADV did not affect the PK of ACN.

**Adefovir Dipivoxil + Trimethoprim/Sulfamethoxazole (Cohort 4)**

By inspection of the plasma concentration-time profiles the following observations can be made with respect to the trimethoprim/sulfamethoxazole (TMP/SMX)-ADV drug interaction study.

- Administration of adefovir dipivoxil alone and in combination with TMP/SMX resulted in similar adefovir concentrations over time (figure 7).
- Administration of TMP/SMX alone and in combination with adefovir dipivoxil resulted in similar trimethoprim concentrations over time (figure 8).
- Administration of TMP/SMX alone and in combination with adefovir dipivoxil resulted in similar sulfamethoxazole concentrations over time (figure 9).

Figure 7: Adefovir Plasma Concentration vs. Time Plot (ADV-TMP/SMX study)



DV PK parameters and applicable statistical comparisons in this drug-drug interaction study are summarized in the following table.

**Plasma Adefovir Pharmacokinetic Parameters Alone and with Trimethoprim/Sulfamethoxazole (n = 18)**

	ADV DP 10 mg Alone (n = 18)	ADV + TMP/SMX (n = 18)	% GMR for ADV DP + TMP/SMX / ADV DP (90% CI)
Geometric Mean $C_{max}$ (ng/mL)	21.73	21.19	97.5 % (89.4 % - 106.4 %)
Geometric Mean $AUC_{(0-\tau)}$ (ng·hr/mL)	208.67	228.16	109.3 % (103.2 % - 115.8 %)
Median $T_{max}$ (hr)	1.04	1.04	-
Median $T_{1/2\lambda_z}$ (hr)	7.38	7.57	-

The ratio of geometric least squares means for adefovir when adefovir dipivoxil was dosed in combination with trimethoprim/sulfamethoxazole versus adefovir dipivoxil alone were approximately 100 % for  $C_{max}$  and  $AUC_{0-\tau}$ . The 90 % confidence intervals around the ratio of geometric means for  $C_{max}$  and  $AUC_{0-\tau}$  were within 89 and 116 %. Therefore, ADV exposure was not affected by TMP/SMX.

Figure 8: Trimethoprim Plasma Concentration vs. Time Plot (ADV-TMP/SMX study)

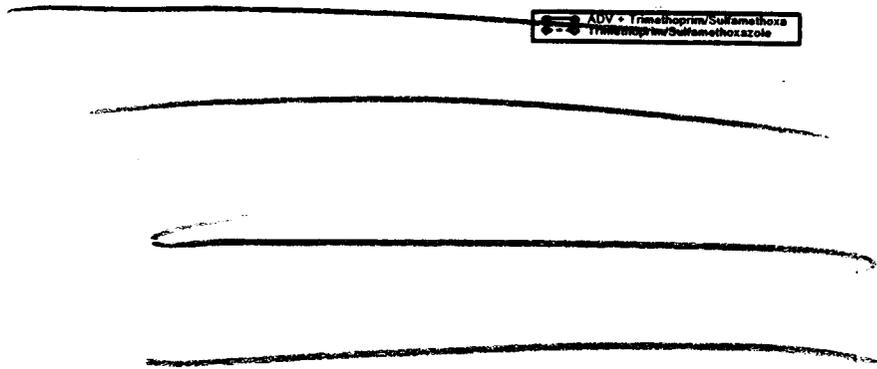
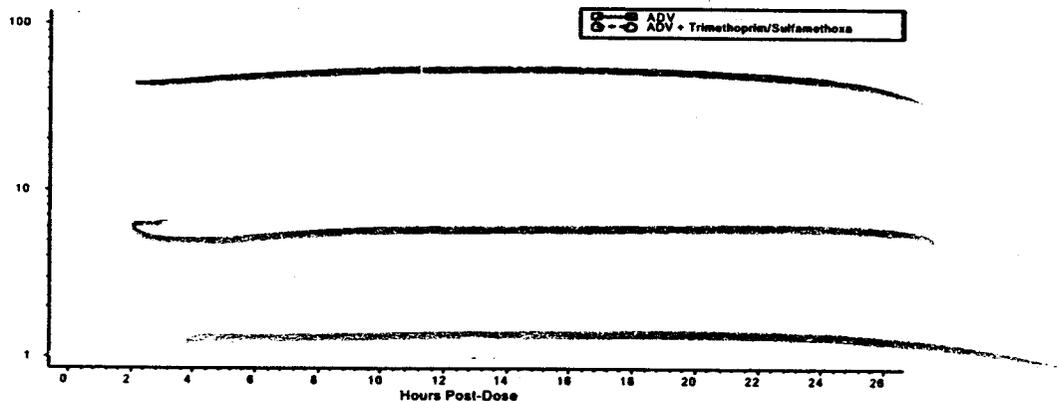


Figure 7: Sulfamethoxazole Plasma Concentration vs. Time Plot (ADV-TMP/SMX study)



The primary trimethoprim PK parameters and applicable statistical comparisons obtained in this study are presented in the following table.

Plasma Trimethoprim Pharmacokinetic Parameters Alone and with Adefovir Dipivoxil (n = 16)

	TMP 160 mg Alone	TMP 160 mg + ADV DP 10 mg	% GMR for TMP/SMX + ADV DP/ TMP (90 % CI)
Geometric Mean $C_{max}$ ( $\mu\text{g/mL}$ )	3.33	3.38	101.3 % (96.6 %-106.3 %)
Geometric Mean $AUC_{(0-\tau)}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	28.17	29.19	103.6 % (97.5 %-110.1 %)
Median $T_{max}$ (hr)	1.28	1.27	-
Median $T_{1/2\lambda_z}$ (hr)	9.53	10.74	-

The GMR for TMP when dosed in combination with ADV DP versus as TMP/SMX alone were approximately 100 % for  $C_{max}$  and  $AUC_{0-\tau}$ . The 90 % confidence intervals around the ratio of geometric means for  $C_{max}$  and  $AUC_{0-\tau}$  were between 96 and 111 %. These findings suggest that ADV did not alter TMP PK.

Sulfamethoxazole PK parameters were not altered in the presence of ADV as shown in the table below.

Plasma Sulfamethoxazole Pharmacokinetic Parameters Alone and with Adefovir Dipivoxil (n = 16)

	SMX 800 mg Alone	Sulfamethoxazole 800 mg + ADV 10 mg	% GMR for TMP/SMX + ADV DP/ SMX (90% CI)
Geometric Mean $C_{max}$ ( $\mu\text{g/mL}$ )	91.4	90.6	99.1% (92.5 %-106.1 %)
Geometric Mean $AUC_{(0-\tau)}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	768.0	806.1	105.0% (99.1 %-111.2 %)
Median $T_{max}$ (hr)	2.2	2.3	-
Median $T_{1/2\lambda_z}$ (hr)	9.7	10.0	-

The GMR (SMX + ADV/SMX) for SMX  $C_{max}$  and  $AUC_{0-\tau}$  were approximately 100 % and the associated 90 % CIs were between 92 and 112 %. These findings indicate that ADV does not affect the exposure of SMX.

#### Overall Conclusions and Recommendations

- Adefovir dipivoxil had no effect on the pharmacokinetics of lamivudine, ibuprofen, acetaminophen, or trimethoprim/sulfamethoxazole.
- Caution should be exercised when adefovir is administered with ibuprofen, because adefovir exposure is increased and both agents are nephrotoxic. The clinical significance of the 30 % increase in adefovir exposure is unknown.
- Administration of multiple doses of adefovir dipivoxil given alone or in combination with lamivudine, ibuprofen, acetaminophen, or trimethoprim/sulfamethoxazole appeared to be safe and well tolerated in these healthy male and female subjects.

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Study Title: A Phase 1, Randomized, Open-Label, Pharmacokinetic Study in Healthy Volunteers to Assess the Effect of Food on the Bioavailability and Pharmacokinetics of the Intended Commercial Formulation of Adefovir Dipivoxil 10 mg Tablets

Study No.: GS-00-476

Study Period: February, 2001

Investigator:

**Study Design:**

This was a 2-period, crossover, randomized, open-label study. There were two treatments:

- Treatment A (reference): subjects received 10 mg ADV in the fasted state.
- Treatment B (test): subjects received 10 mg tablet taken in a fed state (standardized high fat meal).

**Subjects**

A total of 18 subjects completed the study. One subject was excluded from the analysis because the subject's extrapolated area (%AUC extrapolated) under the curve from  $AUC_{0-t}$  to  $AUC_{0-\infty}$  exceeded 30 % in the fed treatment. This exclusion is acceptable.

**Table: Subject Demographics**

Gender	10 males and 8 females
Mean Age in years (range)	29 (18-41)
Mean Weight in kg (range)	71.4 (45.4-93.5)
Mean Height in cm (range)	174 (160-185)
Race	16 Caucasian and 2 Hispanic

**Formulation:** adefovir dipivoxil 10 mg tablet, manufactured by Gilead Sciences, Inc., Lot No. D010C1, manufacturing date October 1, 2000.

**Pharmacokinetics:**

The following ADV pharmacokinetic parameters were determined in the fed and fasted state:  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $T_{max}$ ,  $T_{1/2 \lambda_z}$ ,  $C_{last}$ ,  $CL/F$ ,  $T_{last}$ ,  $kel$ , % AUC extrapolated, and  $V_z/F$ .

**Safety:** Adverse events, laboratory tests, and physical examinations were evaluated.

**Pharmacokinetic Sampling Schedule:**

- Collection of Blood (15 samples): 0/predose, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours post dose
- Collection of Urine samples\* (7 samples): 0/predose void, 0-4, 4-8, 8-12, 12-24, 24-36, 36-48 hours post dose

\* urine samples were not analyzed, but aliquots were stored for possible future analyses.

**Pharmacokinetic/Statistical Analyses:**

The food effect was evaluated using standard PK-statistical methods.

**Assay/Analytical Method:**

A validated bioanalytical method was used to analyze samples for adefovir concentrations.

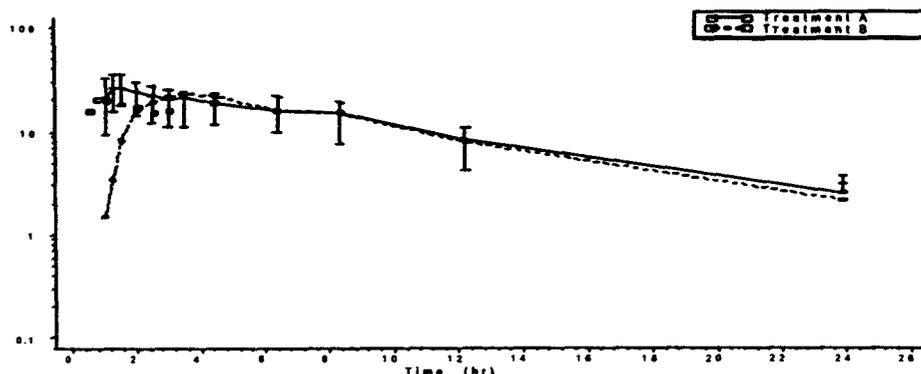
The analysis was performed at

The method was acceptable and had the following characteristics.

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

**Pharmacokinetic Results and Discussion**

The median plasma ADV concentrations versus time profiles for the two treatments are plotted in the figure below.



Inspection of the plot, suggests that the two treatments exhibit similar ADV disposition although the  $T_{max}$  is prolonged in the fed state.

Plasma adefovir pharmacokinetic parameters and statistical comparisons are summarized in Table I.

**Table I: Summary of ADV Pharmacokinetic Parameters in Fasted and Fed States (10 mg adefovir dipivoxil single dose)**

	Fasted (Treatment A)	Fed (Treatment B)	% Geometric Least Squares Means Ratio	Confidence Intervals (90 %) for GMR (fed/fasted)
$C_{max}$ (ng/mL) Mean $\pm$ SD Minimum Maximum	20.8 $\pm$ 3.8	17.7 $\pm$ 3.4	87.4	79.7 – 95.8
$AUC_{0-1}$ (ng•hr/mL) Geometric LSmean Minimum Maximum	177 $\pm$ 40	168 $\pm$ 34	98.8	87.3 – 111.7
$T_{max}$ (hr) Minimum Median Maximum	0.49	1.50	NA	NA

Consumption of a high-fat meal prior to the administration of ADV 10 mg did not alter relative adult AUC. The ratio (fed vs. fasted) of geometric least squares means for  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were approximately 100 %. On the other hand,  $C_{max}$  decreased by approximately 13 %. The 90 % confidence intervals for the ratio of geometric means for  $AUC_{0-t}$  fell within the PK no-effect bounds of 80 % to 125 %, indicating that the food effect was insignificant. The  $C_{max}$  90 % CI (79.7, 95.8) was slightly out of this no-effect range. However, the lower bound is very close to the BE lower limit and this potentially small change in  $C_{max}$  is unlikely to have a significant clinical effect. Several literature reports suggest that for NNRTIs, NRTIs and NTRTIS (nucleotides),  $C_{max}$  may not be as critical as AUC in influencing efficacy. Median  $T_{max}$  was delayed by approximately two hours by food, and is consistent with a delay in gastric emptying due to a meal.

#### **Safety Results**

According to the sponsor, headache was the most frequently reported adverse event (AE). All AEs reported during the study were mild or moderate in severity. There were no serious AEs reported, and no subjects discontinued the study due to AEs. No treatment-related changes in clinical laboratory parameters, vital signs, or physical examinations were observed.

#### **Conclusions and Recommendation:**

Adefovir pharmacokinetic parameters,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$ , were not significantly altered (< 15 % decrease) in the presence of food. Based on these results, adefovir dipivoxil can be administered to patients with or without food.

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# Sample Meals in Food Effect Study

## Study Menu 25545\_1

Comments: HS-CHAD

	Breakfast	Lunch	Dinner	Snack
Fri FEB-09 Day 1		4 OZ CHICKEN 13:00 BREAST ON BUN 0 W/LETTUCE LEAF & TOMATO SLICE 2 T MAYO 4 OZ POTATO SALAD 4 OZ FRUIT COCKTAIL 4 OZ RAINBOW SHERBET MILK, WATER, OR DECAF POP	4 OZ PORK CUTLT 18:30 1 BAKED POTATO 0 4 OZ CORN 3 OZ LETTUC 2 T DRESSING 1 - 1.5 OZ ROLL 4 OZ TAPIOCA PUDDING 3 T MARGARINE 2 T SOUR CREAM MILK, WATER, OR DECAF POP	2 OZ CHEESE 21:30 0 2 OZ CRACKERS 21:30 0 DECAF POP 21:30 0

## Study Menu 25545\_1

Comments: HS-CHAD

	Breakfast	Lunch	Dinner	Snack
Sat FEB-10 Day 2	4 OZ OATMEAL 07:30 1 OZ BR SUGAR 0 2 SLICES TOAST 2 T MARGARINE 2 T JELLY 2 SLICES BACON 4 OZ GRAPE JC 1/2 PT 2% MILK	(HOT HAM & CHZ 13:00 SANDWICH) 0 3 OZ HAM 1 OZ CHEESE 1 4" BUN 4 OZ COLESLAW 4 OZ FRESH FRUT 3X3 LEMON CAKE MILK, WATER, OR DECAF POP	(HOT BEEF 18:30 SANDWICH) 0 3 OZ ROAST BEEF 2 SLICES WHEAT BREAD 4 OZ MASHED POTATOES 4 OZ GRAVY 4 OZ MIXED VEG 1 SLICE APPLE PIE (10 CT) MILK, WATER, OR DECAF POP	1.5 OZ PRETZELS 21:30 0 DECAF POP 21:30 0

**Title**

Single Dose Study to assess the effect of P-glycoprotein (PGP) on the bioavailability and pharmacokinetics of adefovir dipivoxil and tenofovir disoproxil fumarate

**Objective**

Determine the effect of PGP on pharmacokinetics of adefovir and tenofovir following administration of the respective prodrugs

**Study Design (Adefovir)**

A single dose of adefovir dipivoxil 50 mg equivalent/kg was administered to wildtype (WT, FBV strain) and MDR1a<sup>-/-</sup> (PGP knock out mice). Animals were randomly assigned to treatment group. Blood samples were obtained from time 0 hours (predose) to 8 hours post dose. Aggregate plasma concentration-time profiles were obtained using data from three animals per time point. ADV pharmacokinetic parameters were calculated.

**Results**

Following oral administration of ADV DP, ADV was detected in serum within two minutes (first blood sampling point) in both wild type and knock out mice.  $T_{max}$  appeared comparable in the two types of mice; suggesting that PGP expression did not affect the initial rate of drug absorption. In wild type mice  $T_{max}$  occurred within 2 minutes post dose and  $T_{max}$  occurred between 2 and 5 minutes in knock out mice. Because  $T_{max}$  occurred so rapidly, it is likely that its estimation may be accurate. ADV  $C_{max}$  in wild type mice (5000 – 8000 ng/mL) appeared to be lower than in knock out mice (11,000 – 14,000 ng/mL). The reason(s) for the differences in  $C_{max}$  is not clear. On the other hand, AUCs appeared comparable in the two types of mice strains. The AUC values overlapped: AUC (ng·hr/mL) were 9,000 – 22,000 in wild type and 13,000 – 18,000 in knockout mice. The  $C_{8hr}$  appeared similar in the two types of mice with a value of 1000 ng/mL.

**Discussion and Conclusions**

The sponsor concludes: “the absence or presence of PGP does not appear to have a substantial effect on the ADME of adefovir”. This review does not think that any conclusions can be drawn from the study findings, because estimated exposure measures, particularly  $C_{max}$  values may be inaccurate. Thus, subsequent exposure comparisons are inappropriate. It is recognized that animal PK data, especially those obtained using aggregate profiles tend to be highly variable and are often unduly influenced by “outliers”. Additionally, although animal data may provide supportive evidence, these data are not always applicable to humans. In light of the stated limitations of animal studies, a study in humans is required to make any conclusions regarding the role of PGP and any other drug transporters on ADV PK in humans.

**Recommendation**

The role of PGP and other transporters should be evaluated in human subjects because results in this study were inconclusive. Results in humans are required in order to make dosing recommendations.

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**Title**

Inhibition of cytochrome P4501A2, 2C9, 2C19, 2D6, and 3A4 catalytic activities by adefovir and adefovir dipivoxil

**Objective**

To determine whether the test substances, adefovir dipivoxil (ADV DP) and adefovir (ADV) inhibit human cytochrome P450 activity

**Study Design**

The methodology adopted in this study was the typical design for *in vitro* metabolism studies. The study had two parts: 1) range finding analysis to determine the IC<sub>50</sub> of ADV and ADV DP with model substrates and 2) detailed study to determine K<sub>i</sub> of ADV and ADV DP

Enzymes, model substrates, metabolites monitored and controls used in this study were acceptable.

Enzyme	Model enzyme substrate	Metabolite product monitored	Positive Control (known inhibitor)	Concentrations (µM)
CYP1A2	Phenacetin	acetamidophenol	7,8- Benzoflavone	
CYP2C9	Diclofenac	4-hydroxydiclofenac	Sulfaphenazole	
CYP2C19	(S)- mephenytoin	(S)-4-hydroxymephenytoin	Tranylcypromine	
CYP2D6	Bufuralol	1-hydroxybufuralol	Quinidine	
CYP3A4	Testosterone	6β-hydroxytestosterone	Ketoconazole	
CYP3A4	Midazolam	1-hydroxymidazolam	Ketoconazole	
Control microsomes	Added to standardize protein concentration			

**Results**

**Positive Controls**

All positive controls exhibited greater than 80 % inhibition for the specific enzymes, indicating that the test system was functioning adequately.

**Adefovir**

Adefovir did not inhibit any of the enzyme systems tested. The percent inhibitor was zero for all enzymes (values < 0 %) over the ADV concentration range. IC<sub>50</sub> values could not be calculated for adefovir.

**Adefovir Dipivoxil**

Adefovir dipivoxil did not inhibit any of the CYP enzyme systems tested, apart from CYP3A4. The inhibition was substrate dependent. The ADV DP IC<sub>50</sub> values for CYP3A4-midazolam and -testosterone activity were 19 µM and 83 µM, respectively. The mean apparent K<sub>i</sub>s were 9 µM and 45 µM for CYP3A4-midazolam and -testosterone activity respectively.

### Discussion

ADV does not inhibit most common CYP pathways; thus, ADV is not likely to undergo CYP-based metabolic drug-drug interactions in which ADV is an enzyme inhibitor. Likewise, ADV DP is not likely to inhibit CYP most CYP pathways, apart from CYP3A4. However, ADV DP is not present systemically, therefore it will not undergo metabolically based drug-drug interactions in the liver. In theory, the ADV DP concentration in the gut (10 mg dose in assumed 250 mL volume) immediately after dosing is comparable in magnitude to the  $K_i$  values obtained in this *in vitro* metabolism study. Therefore, ADV DP may inhibit gut metabolism of 3A4 substrates. However, conversion of ADV DP to ADV is rapid (ADV detectable within 30 minutes) suggesting that high ADV DP concentrations in the gut will be transient. In effect, drug-drug interactions due to CYP3A4 inhibitor by ADV DP are unlikely. Based on a comparison of  $K_i$  values it appears that ADV DP is an extremely weak CYP3A4 inhibition. The  $K_i$  of ADV DP is relatively high compared to ritonavir ( $K_i = 0.02 \mu\text{M}$ ) which is a potent CYP3A4 inhibitor.

### Conclusions

ADV and ADV DP are not likely to inhibit the metabolism of drugs metabolized by the CYP450 enzyme system.

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