OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-449	Submission Date(s): June 22, 2007
Brand Name	Hepsera® Tablets
Generic Name	Adefovir Dipivoxil
Reviewer	Shirley K. Lu, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND division	DAVP
Sponsor	Gilead
Relevant IND(s)	21-449
Submission Type; Code	SE5-011 (Pediatric Efficacy Supplement)
Formulation; Strength(s)	Tablet, 10 mg
Indication	For the treatment of chronic hepatitis B in adults and adolescents

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1 Executive Summary

Adefovir dipivoxil (Hepsera®) is the diester prodrug of adefovir. The active metabolite (adefovir diphosphate) inhibits HBV DNA polymerase. Adefovir is approved for treatment of hepatitis B virus infection in adults with adequate and impaired renal function. There is currently no pediatric indication or dosing recommendations.

Study **GS-02-515** demonstrated bioequivalence in adults between the tablet and initial oral suspension formulation (A). Formulation A was then used in a dose finding study for safety and efficacy evaluation in pediatric subjects ages 2 to <18 (**GS-02-517**). However, the composition of formulation A was changed slightly to improve palatability. Subsequently, study **GS-02-536** demonstrated bioequivalence in adults between the tablet and the second oral suspension formulation (B). **GS-US-103-0518** is the phase 3 study investigating safety and efficacy of the final oral suspension formulation (B) in pediatric patients ages 2 through <12 and tablets in adolescents 12 to <18.

Dosing recommendations for drugs to treat HBV in pediatric patients must be supported by clinical efficacy and safety data. Significantly more patients from the 12 to <18 age group treated with adefovir achieved the primary efficacy endpoint at the end of 48 weeks blinded treatment (23%) when compared to placebo-treated patients (0%). The proportion of patients from the two lower age groups (ages 2 to <12) who responded to treatment with adefovir was not statistically significant when compared to the placebo arm, although the exposure of adefovir in these patients was comparable to that observed in older patients.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the pediatric pharmacokinetic data submitted in the sNDA. The presented information is acceptable and supports the use of the 10-mg tablet in adolescent patients ages 12 to <18 years old.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Four studies have been conducted in support of this pediatric efficacy supplement.

GS-02-515

"A Phase 1, Randomized, Open-Label Pharmacokinetic Study in Healthy Volunteers to Evaluate the Bioequivalence Between an Oral Suspension and the Tablet Formulation of Adefovir Dipivoxil."

In this study, a total of 22 adult subjects were evaluated for bioequivalence between the tablet and oral suspension formulation A. Subjects were given 5 mL of the 2 mg/mL suspension or a single 10-mg tablet and crossed over after a 7 day washout period. The test vs. reference 90% CI, (point estimate) were: AUC_{0-t}: 0.933-1.07 (1.00), C_{max}: 0.946-1.12 (1.03), AUC_{inf}: 0.944-1.08 (1.01). Thus, the two formulations were deemed bioequivalent.

GS-02-517

"A Phase 1-2 Open-Label Study of the Pharmacokinetics and Safety of a Single Dose of Adefovir Dipivoxil in Children and Adolescents (age 2-17) with chronic Hepatitis B."

The purpose of the study was to determine an appropriate dose of oral suspension to be further evaluated for safety and efficacy in pediatric patients. This study evaluated pharmacokinetics of a single dose of adefovir at two different doses levels for the 2-6 and 7-11 year olds and one dose level for the 12-17 year olds. All subjects received the oral suspension formulation A. The following description represents the treatments and doses administered to each age group. NOTE: For simplicity, the age group with children between ages 2 to <7 will be referred to as "2-6" and ages 7 to <12 will be referred to as "7-11" and 12 to <18 years will be referred to as "12-17" for the remainder of the review.

0.14 mg/kg oral suspension	0.3 mg/kg oral suspension	10 mg oral suspension
2-6 yr. old: 12 subjects	2-6 yr. old: 12 subjects	12-17 yr. old: 15 subjects
7-11 yr. old: 18 subjects	7-11 yr. old: 18 subjects	

The results of the study indicated that the 0.3 mg/kg dose was appropriate for the 2-6 year olds; however, a 0.25 mg/kg dose was most appropriate for 7-11 year olds (based on predicted exposures compared to exposures in adults).

Table 1

Mean (± SD) Pharmacokinetic Pharameters of Adefovir in Adult and Pediatric Hepatitis Patients

	Pharmacokinetic Parameter		
Population	C_{max} (ng/mL)[a]	C_{last} (ng/mL)[a]	$AUC_{0-\infty}$[a]
2–6 yrs (0.3 mg/kg) (n = 12)	26.93 (7.86)	2.40 (0.98)	224.13 (78.72)
7–11 yrs (0.3 mg/kg (n = 18)	33.08 (8.56)	2.70 (1.12)	292.44 (101.94)
7–11 yrs (0.3 mg/kg)[b]	30.89 (7.35)	–	273.29 (87.01)
7–11 yrs (0.25 mg/kg)[c]	25.74	–	227.74
12–17 yrs 10 mg (n = 15)	22.75 (4.62)	2.70 (1.03)	237.30 (56.95)
Study GS-00-472 Adult patients 10 mg tablet (n = 14)	18.36 (6.26)	3.24 (1.54)	230.34 (69.99) [189.6-251.1]

a Mean (SD) [90% confidence interval]

b data normalized to 10 mg only for patients receiving > 10 mg dose

c Predicted Data for a 0.25 mg/kg dose

GS-02-536

"A Phase 1, Pharmacokinetic Study in Healthy Volunteers to Evaluate the Bioequivalence of an Oral Suspension Formulation and the Tablet Formulation of Adefovir Dipivoxil."

This phase 1, SD, crossover bioequivalence study evaluated PK of the re-formulated ADV suspension (formulation B) and marketed tablet in healthy adults. Upon completion of GS-02-517, formulation A was re-formulated to improve palatability. A total of 17 subjects were evaluated for bioequivalence between the tablet and oral suspension formulation B. Subjects were given 5 mL of the 2 mg/mL suspension or a single 10-mg tablet and crossed over after a 7 day washout period. The 90% CI, (point estimate) were: AUC_{0-t}: 0.89-1.02 (0.95), C_{max}: 0.81-0.95 (0.88), AUC_{inf}: 0.90-1.03 (0.96). Thus, the two formulations were deemed bioequivalent and formulation B was used in study GS-US-103-0518.

GS-US-103-0518

"A phase 3 Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (age 2 to <18) with Chronic Hepatitis B."

This phase 3, 48-week efficacy and safety study in pediatric patients was conducted with the following age groups and doses (N=173 total):

2-6 yr. old	7-11 yr. old	12-17 yr. old
0.3 mg/kg oral suspension	0.25 mg/kg oral suspension	10 mg tablet

There were two treatment periods for this study. The first period was 48 weeks, placebo-controlled, double-blind, parallel group, randomized at a 2:1 ratio to adefovir or placebo. After 44 weeks, patients with no seroconversion were offered the opportunity to come back for a 192-week open-label adefovir treatment period. The PK parameters are summarized in the table below:

Table 2

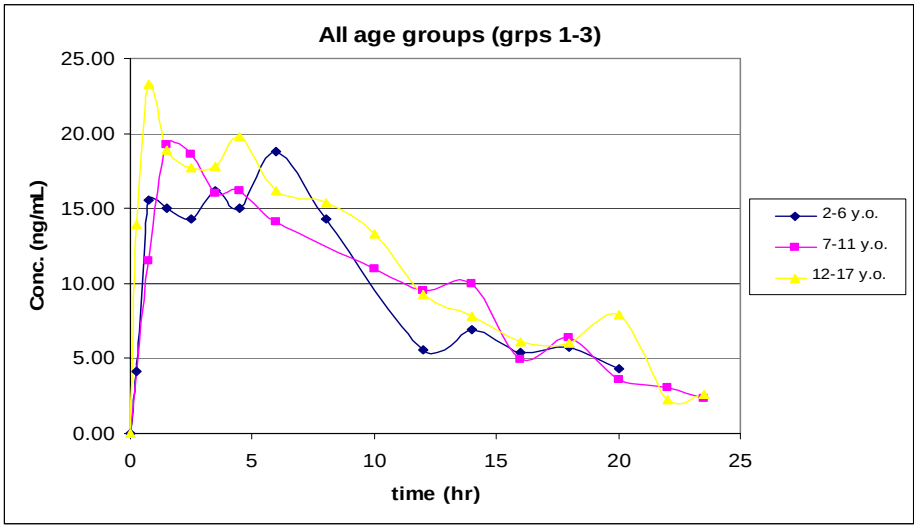
Study Age Group	Pharmacokinetic Parameter	
	C_{max} (ng/mL)	AUC_{tau} (ng•h/mL)
GS-US-103-0518		
2–6 years (0.3 mg/kg suspension)[a]	17.09	210.37
7–11 years (0.25 mg/kg suspension)[a]	18.47	222.09
12–17 years (10-mg tablet)[a]	21.96	248.76
Study GS-00-472		
Adults (10 mg tablet)[b]	19.71 (8.15)	215.75 (78.61)

GS-US-103-0518 analysis used the pharmacokinetics analysis set

All age groups exhibited similar Cmax and AUC exposures to the historical adult values (based on the approved adult dose of 10 mg q.d.). Population PK methods were used to calculate PK parameters for the pediatric patients. The report did not include AUC or Cmax estimates for individual subjects. Concentrations around the same timepoint for the same subject did not differ significantly over the course of the study (between weeks 4, 8, 12, 24, 36, and 48) with no

evidence that exposure decreased over time. Figure 1 shows the similarity between the plasma concentration vs. time curves for all three age groups.

Figure 1



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2 Question Based Review

2.1 General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Hepsera® tablets were approved for use in adults on September 20, 2002. On June 22, 2007, Gilead submitted an sNDA-Efficacy Supplement- to the FDA for review. This supplement seeks an indication for the use of Hepsera® in adolescent patients age 12 to <18 years,

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Adefovir dipivoxil (Hepsera®) is the diester prodrug of adefovir. The active metabolite (adefovir diphosphate) inhibits HBV DNA polymerase.

INDICATION
Hepsera is indicated for the treatment of chronic hepatitis B in adults with evidences of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

This indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function, and in adult patients with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The sponsor is seeking an indication of use for the 10-mg oral tablet dosage form of Hepsera® in adolescent patients (12 to <18 years of age).

The current recommended dosage is as follows:

The recommended dose of HEPSERA in chronic hepatitis B patients with adequate renal function is 10 mg, once daily, taken orally, without regard to food. The optimal duration of treatment is unknown.

Dose Adjustment in Renal Impairment:

Significantly increased drug exposures were seen when HEPSERA was administered to patients with renal impairment **(see Pharmacokinetics)**. Therefore, the dosing interval of HEPSERA should be adjusted in patients with baseline creatinine clearance <50 mL/min using the following suggested guidelines (see Table 3). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated.

Additionally, it is important to note that these guidelines were derived from data in patients with pre-existing renal impairment at baseline. They may not be appropriate for patients in whom renal insufficiency evolves during treatment with HEPSERA. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 3 **Dosing Interval Adjustment of HEPSERA in Patients with Renal Impairment**

	Creatinine Clearance (mL/min)*			
	≥50	20–49	10–19	Hemodialysis Patients
Recommended dose and dosing interval	10 mg every 24 hours	10 mg every 48 hours	10 mg every 72 hours	10 mg every 7 days following dialysis

* Creatinine clearance calculated by Cockcroft-Gault method using lean or ideal body weight.

The pharmacokinetics of adefovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There were two studies that were conducted in pediatric patients:

-The first study (GS-02-517) was a single-dose, crossover design to identify the most appropriate dose for children ages 2-6 (N=12), 7-11 (N=18), and 12-17 (N=15). The doses used in this study were 0.14 mg/kg and 0.3 mg/kg of oral suspension for the two lower age groups and 10 mg of the oral suspension for the oldest age group.

-The second study (GS-US-103-0518) was a phase 3, 48-week, double-blind, placebo-controlled safety and efficacy study in the same age groups of children as the first study (N=173 subjects randomized and treated, N=170 subjects completed). The doses selected for use in this study were determined from the results of study GS-02-517. The doses were: ages 2-6: 0.3 mg/kg/day oral suspension, ages 7-11: 0.25 mg/kg/day oral suspension, ages 12-17: 10 mg tablet/day.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The sponsor's primary endpoint was:

- The proportion of subjects with serum HBV DNA <1000 copies/mL and normal ALT at week 48.

The sponsor's secondary endpoints were:

- The observed change from baseline values for HBV DNA (log10 copies/mL) by study visit
- The observed change from baseline values for ALT (U/L) by study visit
- The proportion of subjects with HBV DNA <1000 copies/mL by study visit
- The proportion of subjects at week 48 with HBV DNA <lower limit of quantitation (LLQ), <400, <1000, <10,000, and ≥10,000 copies/mL, respectively.
- The proportion of subjects with normal ALT by study visit
- The proportion of subjects with HBe antigen loss (defined as having negative serum HBeAg for subjects with positive serum HBeAg at baseline) by study visit
- The proportion of subjects with HBeAg seroconversion (defined as having negative serum HBeAg and positive serum anti-HBe for subjects with positive serum HBeAg at baseline) by study visit
- The proportion of subjects having HBV DNA < 1000 copies/mL, normal ALT, and HBeAg seroconversion out of the subset of subjects with HBeAg+ at baseline by study visit
- The proportion of subjects with HBs antigen loss (defined as having negative serum HBsAg for subjects with positive serum HBsAg at baseline) by study visit

The primary efficacy endpoint for the two pivotal studies in adults (for approval of the original NDA) was improvement in liver biopsy histology at week 48 compared with baseline (studies GS-98-437 and GS-98-438). Although historically, the Division of Antiviral Products (DAVP) has required histologic endpoints in the efficacy analysis of drugs for the treatment of chronic HBV, the policy changed based on discussion at an advisory committee meeting in August 2002. During the course of the review for Tyzeka® (Telbivudine), it was decided that therapeutic response can serve as a primary endpoint and histologic response as a key secondary endpoint. This decision was made due to major limitations of the liver biopsy procedure (including risk to the patient) and a lack of a clear correlation between the inflammatory score and clinical outcome.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Adefovir concentrations in human plasma and urine samples were determined by validated liquid chromatographic methods using LC/MS/MS. The assays are acceptable.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy?

From the original NDA review, exposure response relationships have not been established between adefovir exposure and efficacy. However, based on the sponsor's hyperbolic function 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-mg and 60-mg doses. The sponsor's modeling show that the 20-mg dose would be more effective than the 10-mg dose.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety?

Based on empirical information, the 30-mg dose produces mildly reversible nephrotoxicity whereas the 10-mg dose rarely produced nephrotoxicity in subjects with adequate renal function. Doses between 10 mg and 30 mg have not been studied.

2.3 Intrinsic Factors

Based on Dr. Robert Kumi's original review of this NDA, the only evaluable intrinsic factor that affects adefovir exposure and requires dose modification is renal function (degree of renal impairment). Gender did not affect adefovir exposure. The effects of age or race on adefovir exposure could not be assessed due to insufficient data. Based on a hepatic impairment study, impaired hepatic function (determined by Child Pugh score) did not significantly affect adefovir PK. However, two conclusions can be drawn from the hepatic impairment study: 1.) the half-life increases with impaired hepatic function and 2.) subjects who have both impaired renal function and hepatic function are likely to have increased exposures relative to subjects with the same degree of impairment of either function alone.

For further details, please refer to the original NDA review.

2.4 Extrinsic Factors

Food did not significantly affect adefovir exposure, thus, adefovir dipivoxil can be administered without regard for meals.

Concerning drug-drug interactions, based on in vitro metabolism and in vivo drug-drug interaction information, adefovir has a low potential to undergo metabolic drug-drug interactions.

For further details, please refer to the original NDA review.

2.5 General Biopharmaceutics

Adefovir dipivoxil is classified as a BCS Class 3 drug due to its high solubility and low permeability. Solubility and permeability (Caco-2 cells) data regarding the BCS classification were reviewed . For further details, please refer to the original NDA review.

2.6 Analytical Section

Adefovir concentrations in human plasma and urine samples were determined by validated liquid chromatographic methods using LC/MS/MS. The assays are acceptable. For further details, please refer to the original NDA review.

3 Appendices

3.1 Labeling Recommendations

-Under Section 8.4 Pediatric Use (under USE IN SPECIFIC POPULATIONS), the following wording is recommended for the last sentence of the first paragraph

-Under section 12.3 Pediatric Patients (under PHARMACOKINETICS), the following wording is recommended:

"*The pharmacokinetics of adefovir were assessed from drug plasma concentrations in 53 HBeAg positive hepatitis B adolescent patients with compensated liver disease. The exposure of adefovir following 48 weeks of daily administration with 10 mg adefovir dipivoxil tablet in adolescents aged ≥12 to <18 years (C_{max} = 23.33 ng/mL and AUC_{0-24} = 248.76 ng*hr/mL) was comparable to that observed in adult patients."*

3.2 Individual Study Reviews

GS-02-515

1. Title

"A Phase 1, Randomized, Open-Label Pharmacokinetic Study in Healthy Volunteers to Evaluate the Bioequivalence Between an Oral Suspension and the Tablet Formulation of Adefovir Dipivoxil."

2. Objectives

The objectives of this study were:

- To evaluate the PK parameters of a 10 mg dose of adefovir dipivoxil when given as either an oral suspension or a tablet formulation under fasting conditions

- To establish bioequivalence between the tablet and oral suspension, allowing for interchangeability between the two formulations

3. Study Design

This study was a phase 1, randomized, single dose, two-way crossover, open-label PK study. A total of 22 adult subjects were evaluated for bioequivalence between the tablet and oral suspension formulation. Subjects were given 5 mL of the 2 mg/mL suspension or a single 10-mg tablet and crossed over after a 7 day washout period and overnight fast.

4. Sample Collection

A total of 16 blood samples of 5 mL each were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

5. Results

The following excerpt is the sponsor's study results and synopsis of the PK portion of the first BE study. As the 90% CI values for all three parameters were within 80-125%, the oral suspension and tablet are bioequivalent. The sponsor's conclusions are acceptable.

Pharmacokinetic Results: The primary objective of this study was to evaluate the pharmacokinetic parameters of a 10 mg dose of adefovir dipivoxil when given as either an oral suspension formulation or a tablet formulation, administered under fasted conditions. Oral administration of 10 mg adefovir dipivoxil as 5 mL of a 2 mg/mL oral suspension or as a single 10 mg adefovir dipivoxil tablet resulted in equivalent systemic exposures of adefovir as measured by C_{max} and AUC. Point estimates for geometric mean ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 103, 100, and 101%, respectively, with 90% confidence intervals falling within bioequivalence bounds for all three parameters (C_{max} CI of 94.6, 112; AUC_{0-t} CI of 93.3, 107, and $AUC_{0-\infty}$ CI of 94.4, 108).

6. Conclusions

Conclusion: The tablet and oral suspension formulations of adefovir dipivoxil are bioequivalent. Adefovir dipivoxil oral suspension and tablets may be used interchangeably.

Study GS-02-536

1. Title

"A Phase 1, Pharmacokinetic Study in Healthy Volunteers to Evaluate the Bioequivalence of an Oral Suspension Formulation and the Tablet Formulation of Adefovir Dipivoxil."

2. Objectives

The objectives of this study were:

- To evaluate the PK parameters of a 10 mg dose of adefovir dipivoxil when given as either an oral suspension or a tablet formulation under fasting conditions

- To establish bioequivalence between the tablet and the re-formulated oral suspension

3. Study Design

This study was a phase 1, randomized, single dose, two-way crossover, open-label PK study. A total of 17 adult subjects were evaluated for bioequivalence between the tablet and re-formulated oral suspension. Subjects were given 5 mL of the 2 mg/mL suspension or a single 10-mg tablet and crossed over after a 7 day washout period and overnight fast.

4. Sample Collection

A total of 16 blood samples of 5 mL each were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

5. Results

The following is the sponsor's study results and synopsis of the PK portion of the second BE study. As the 90% CI values for all three parameters are within 80-125%, the re-formulated oral suspension and the tablet formulation are bioequivalent. The sponsor's conclusions are acceptable.

Pharmacokinetics Results: Plasma versus concentration time curves revealed comparable adefovir plasma concentration profiles for the adefovir dipivoxil (ADV) suspension and tablet formulations. The maximum plasma concentrations (C_{max}) for both treatments occurred at approximately 1 hour (T_{max}) after dose administration.

Mean C_{max} was approximately 12% lower following administration of the adefovir dipivoxil oral suspension formulation than following administration of the adefovir dipivoxil tablet formulation (20.76 vs. 23.66 ng/mL, respectively). Mean results for other PK parameters were comparable for the adefovir dipivoxil oral suspension as compared to the tablet formulations as follows: $AUC_{0-\infty}$: 197.44 vs. 203.38 ng•hr/mL; AUC_{0-t}: 182.18 vs. 189.78 ng•hr/mL; $\%AUC_{0-\infty}$: 8 vs. 7%; and $t_{½}$: 5.97 vs. 5.81 hours, respectively.

From the firm's calculations, $\%AUC_{0-\infty} = 1-(AUC_{0-t}/AUC_{0-\infty})$

Results of the assessment of bioequivalence are presented below. The data show that the 90% confidence interval (CI) of the ratios of the test/reference treatment were within 80-125%, confirming that the adefovir dipivoxil oral suspension and the tablet formulations are bioequivalent.

Parameter	LS Means		Ratio[a]	90% CI[b]
	Test n = 17	Reference n = 17		
$AUC_{0-\infty}$	190.7	198.0	0.96	0.90-1.03
AUC_{0-t}	175.3	184.5	0.95	0.89-1.02
C_{max}	20.25	23.08	0.88	0.81-0.95

a The ratio of the geometric least-squares (LS) means of the test to reference formulations where test is adefovir dipivoxil oral suspension formulation (Treatment A) and reference is adefovir dipivoxil tablet formulation (Treatment B).

b The confidence interval (CI) is calculated based on the least-squares means differences (natural logarithm scale) back transformed to the original measurement scale.

6. Conclusions

The mean plasma concentration versus time curves of adefovir tablet and oral suspension are superimposable. The 90% confidence intervals for the ratios of adefovir dipivoxil oral suspension/tablet $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were within the range of 80-125%, demonstrating that the two formulations were bioequivalent. Both formulations were well tolerated.

GS-02-517

1. Title

"A Phase 1-2 Open-Label Study of the Pharmacokinetics and Safety of a Single Dose of Adefovir Dipivoxil in Children and Adolescents (age 2-17) with chronic Hepatitis B."

2. Objectives

The objectives of this study were:

- To characterize the PK profile of adefovir dipivoxil 0.14 mg/kg and 0.3 mg/kg in children 2-6 years and 7-11 years of age, including dose proportionality of adefovir dipivoxil liquid formulation.
- To characterize the PK profile of adefovir dipivoxil 10 mg administered as an oral liquid in adolescents 12-17 years of age.

3. Study Design

GS-02-517 was a single-dose, open-label study in children and adolescents with chronic HBV. Subjects had compensated liver disease and were HBeAg-positive and serum HBV DNA (≥ 1 x 10^5 copies/mL) positive at screening.

Upon enrollment, subjects were divided into one of 3 groups depending on age: 2 to <7 y.o., 7 to <12 y.o., and 12 to <18 y.o. Thirteen subjects were enrolled in the 2-6 group, 19 subjects were enrolled in the 7-11 group, and 15 subjects enrolled in the 12-17 group (total of 47 enrolled). One subject for each of the lower age groups discontinued and were not included in the PK analysis. One subject discontinued from the 12-17 group but completed both PK assessment periods and is thus included in the PK analysis.

Subjects in the two lower age groups (ages 2-11) received two single-dose treatments of 0.14 mg/kg and 0.3 mg/kg in a crossover manner. Subjects in the 12-17 group received a single 10 mg dose of the oral suspension formulation. All doses were administered after a minimum of 8 hours of fasting.

4. Rationale for Doses Used in the Trial

The current recommended dosage for adults is 10 mg administered once daily. For an average 70-kg adult, this corresponds to approximately 0.14 mg/kg. The sponsor hypothesized that children may need higher doses to achieve similar exposures as adults, thus the 0.3 mg/kg dose (~2x the adult dose) was also included in the study. Since adolescents 12-17 years old are likely to have similar clearance as adults (and therefore similar exposures), they received a single fixed dose of 10 mg oral suspension.

5. Drugs Used in the Trial

The original oral suspension formulation (A) was used in this study.

6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood and urine samples were collected to assess adefovir drug levels. Blood samples were collected at: pre-dose, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. Urine was collected at pre-dose, 0-4, 4-8, 8-12, and 12-24 hours post-dose.

Bioanalysis

Analytical services were provided by
using a validated LC/MS/MS assay. A linear calibration curve was obtained for standard concentrations between with an LLOQ of . Accuracy ranged from of nominal, while precision (%RSD) ranged from . QC

concentrations were and A total of 675 human plasma samples were analyzed in 11 batches. All batches met the acceptance criteria.

Reviewer's Note
-The assay validation and methodology is acceptable.

Pharmacokinetic Assessments

Primary PK parameters for adefovir were assessed by the application of a non-linear curve fitting method using noncompartmental methods. The method was used with input values for time of dose, plasma adefovir concentration and corresponding real-time values based on drug dosing times whenever possible. Pre-dose sample times of less than time zero were converted to zero. Samples that were below the limit of quantitation (BLQ) prior to Cmax, were treated as zero. BLQ at all other time points were treated as missing data.

Statistical Analysis

The PK statistical analysis included all subjects who received study drug and participated in at least one PK study visit and who had a PK profile deemed evaluable by Gilead.

7. Results

Following oral administration of adefovir dipivoxil, adefovir was detected in plasma following the first sampling timepoint at 0.5 hr. Following 0.14 mg/kg and 0.3 mg/kg doses of adefovir in the 2-6 years age group, mean Cmax values were 14.5 and 26.9 ng/mL, respectively, and mean AUC_{inf} values were 104.7 and 224.1 ng*hr/mL, respectively (see Table 4). The mean concentration of adefovir at 24 hours (C_{last}) was 2.4 ng/mL indicating that there is still circulating adefovir in the body after 24 hours post-dose.

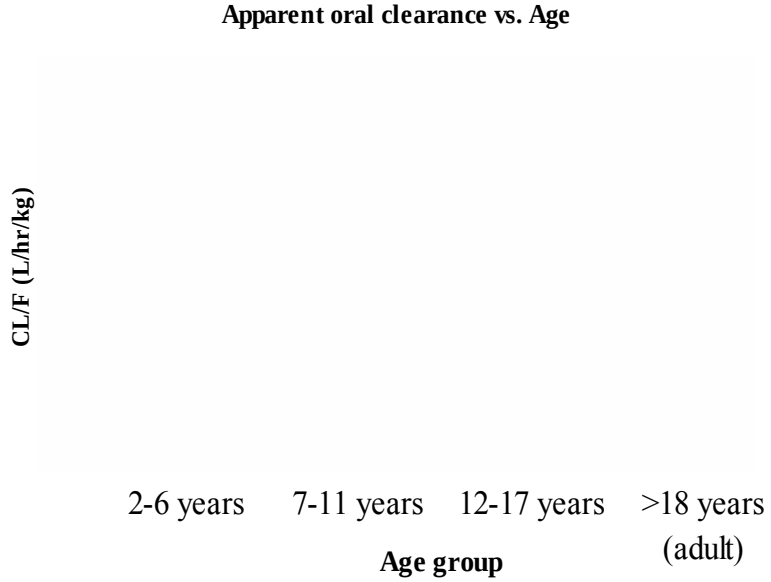
For the 7–11 age group, the mean Cmax values of adefovir following the 0.14 and 0.3 mg/kg doses were 14.1 and 33.0 ng/mL, respectively, and the mean AUC_{inf} values were 128.5 and 292.4 ng*hr/mL, respectively. Due to the weight of seven subjects (3002, 3006, 3008, 3011, 3015, 3017, and 3019) in the 7–11 age group, these subjects received doses greater than 10 mg. Normalizing exposure in these patients to a 10 mg dose resulted in a group mean AUC_{inf} of 273.3 ng*hr/mL.

For the 12–17 age group, the mean Cmax and AUC_{inf} of adefovir following a 10 mg dose were 22.8 ng/mL and 237.3 ng*hr/mL. These values are similar to those observed in adult patients with chronic hepatitis (Gilead study GS-00-472, Cmax=18.4 ng/mL and AUC_{inf} =230.3 ng*hr/mL). The median half-life of adefovir was 6.9 hours. In summary, the pharmacokinetics of adefovir following a 10-mg oral suspension dose in the 12-17 age group were similar to that observed in adults.

Body weight-corrected apparent oral clearance (CL/F) for adefovir was highest for the lowest age group (L/hr/kg) with declines of approximately 30-37% between each adjacent group.

According to the original NDA review, the adult CL/F at week 2 was L/hr/kg. Figure 2 below shows the relationship between age and apparent oral clearance.

Figure 2



All weight-corrected clearance values were based on individual subject weights (not an average for the entire age group). The numbers in each group were: 2-6 years, N=12; 7-11 years, N=18; 21-17 years, N=15.

Table 4

Single-Dose Adefovir Pharmacokinetic Parameters in Children and Adolescents (Aged 2-17) with Chronic Hepatitis B

Pharmacokinetic Parameter	2-6 Years (N = 12)		7-11 Years (N = 18)		12-17 Years (N = 15)
	0.14 mg/kg	0.3 mg/kg	0.14 mg/kg	0.3 mg/kg	10 mg
AUC_{0-t} (ng*h/mL)					
Mean (± SD)	86.06 (32.70)	202.43 (70.14)	114.42 (53.60)	265.83 (94.12)	211.17 (52.92)
Median	86.65	219.90	118.85	266.90	216.90
Min-Max	28.0-131.4	34.2-290.1	31.0–247.9	70.6–476.2	114.2–296.2
$AUC_{0-\infty}$ (ng*h/mL)					
Mean (± SD)	104.74 (33.76)	224.13 (78.72)	128.48 (53.81)	292.44 (101.94)	237.30 (56.96)
Median	108.35	237.20	128.25	287.45	234.10
Min-Max	46.9–158.8	40.9–343.8	51.1–274.5	78.4–535.2	147.2–329.8
C_{max} (ng/mL)					
Mean (± SD)	14.48 (5.27)	26.93 (7.86)	14.12 (4.61)	33.03 (8.56)	22.75 (4.62)
Median	14.15	26.90	14.25	32.40	22.50
Min-Max	7.39–26.70	7.68–39.90	5.34–21.50	11.50–49.30	16.40–30.00

Figure 3

Median Plot of Adefovir Dipivoxil Plasma Concentrations (Linear Scale)

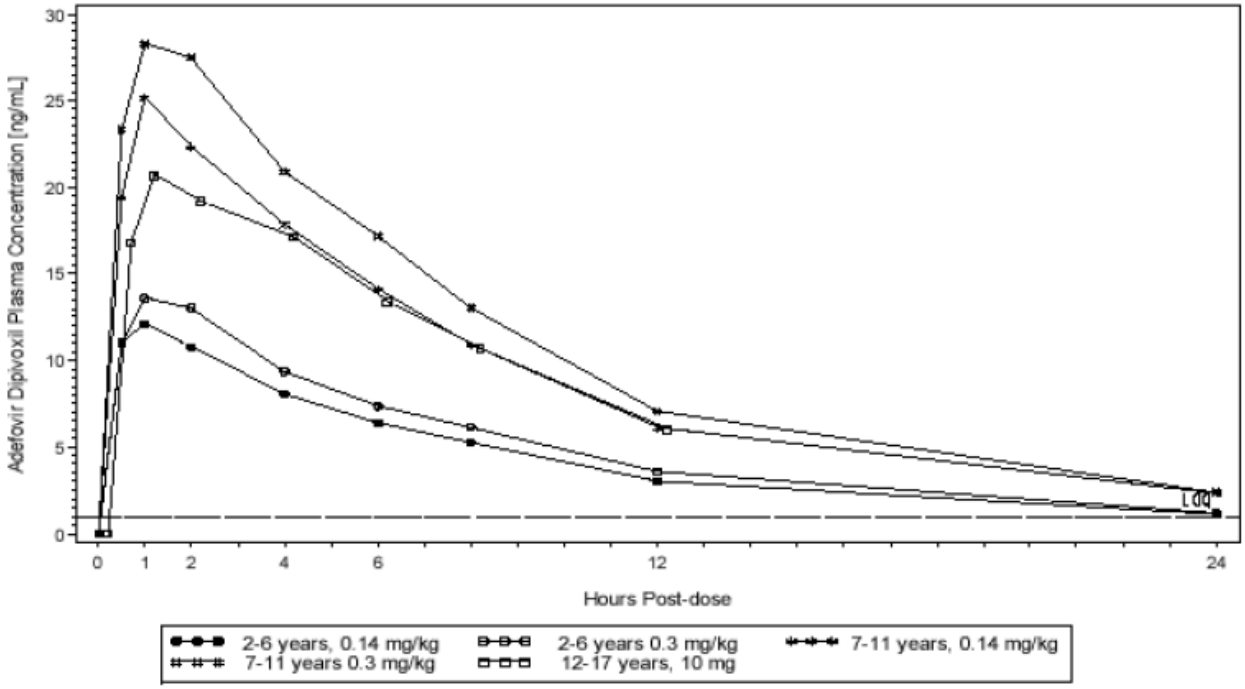


Table 5

Mean (± SD) Pharmacokinetic Pharameters of Adefovir in Adult and Pediatric Hepatitis Patients

Population	Pharmacokinetic Parameter		
	C_{max} (ng/mL)[a]	C_{last} (ng/mL)[a]	$AUC_{0-\infty}$[a]
2–6 yrs (0.3 mg/kg) (n = 12)	26.93 (7.86)	2.40 (0.98)	224.13 (78.72)
7–11 yrs (0.3 mg/kg (n = 18)	33.08 (8.56)	2.70 (1.12)	292.44 (101.94)
7–11 yrs (0.3 mg/kg)[b]	30.89 (7.35)	–	273.29 (87.01)
7–11 yrs (0.25 mg/kg)[c]	25.74	–	227.74
12–17 yrs 10 mg (n = 15)	22.75 (4.62)	2.70 (1.03)	237.30 (56.95)
Study GS-00-472 Adult patients 10 mg tablet (n = 14)	18.36 (6.26)	3.24 (1.54)	230.34 (69.99) [189.6-251.1]

a Mean (SD) [90% confidence interval]

b data normalized to 10 mg only for patients receiving > 10 mg dose

c Predicted Data for a 0.25 mg/kg dose

8. Conclusions

In children 2-6 and 7-11 years of age, the adefovir exposure increased in an approximately dose-proportional manner. Based on the PK data at both doses (0.14 mg/kg/day vs. 0.3 mg/kg/day), the 0.3 mg/kg/day dose most closely matched adult (and the 12-17 year group) exposures for the 2-6 years age group. Thus, the 0.3 mg/kg/day dose was selected for the 2-6 age group. The 7-11 age group experienced higher than adult exposures with the 0.3 mg/kg/day dose while the 0.14 mg/kg/day dose gave exposures that were too low. Based on modeling and estimates, a dose of 0.25 mg/kg/day was selected for further evaluation in the 7-11 age group. For the 12-17 age group, a 10 mg per day dose was selected.

GS-US-103-518

1. Title

"A phase 3 Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (age 2 to <18) with Chronic Hepatitis B."

2. Objectives

The objectives of this study were:

- To investigate the efficacy of adefovir dipivoxil for the treatment of CHB in children and adolescents (age 2 to <18) compared to placebo following 48 weeks of treatment.
- To investigate the safety of adefovir dipivoxil for the treatment of CHB in children and adolescents (age 2 to <18) compared to placebo following 48 weeks of treatment.

- To evaluate the proportion of children and adolescents who experience HbeAg and HbsAg seroconversion following 48 weeks of treatment with adefovir dipivoxil or placebo.

- To evaluate the development of conserved site mutation associated with resistance to adefovir dipivoxil.

- To evaluate the safety (including assessment of growth and renal function) and efficacy of adefovir dipivoxil in children and adolescents for up to 5 years.

3. Study Design

Study GS-US-103-0518 is an ongoing multicenter study evaluating adefovir dipivoxil in treatment-naïve and treatment experienced pediatric subjects with CHB. There are two treatment periods in this study. The first one is complete and consisted of 48 weeks of a double-blind, placebo-controlled, parallel-group treatment period. Visits occurred at weeks 12, 24, 36, 44, and 48. Randomization occurred in a 2:1 treatment:placebo ratio. Dosing for the first treatment period was as follows:

- For subjects 2 to <7 years: 0.3 mg/kg once daily (or matching placebo)
  - Adefovir N=23; Placebo N=12
- For subjects ≥7 to <12 years: 0.25 mg/kg once daily (or matching placebo)
  - Adefovir N=36; Placebo N=19
- For subjects ≥12 to <18: 10 mg once daily (or matching placebo)
  - Adefovir N=53; Placebo N=27

At the end of this initial double-blind treatment, adefovir dipivoxil treated and placebo treated subjects who did not exhibit HbeAg or HbsAg seroconversion at week 44 were offered the opportunity to enter into an open-label adefovir dipivoxil treatment period lasting up to 192 weeks. Placebo-treated subjects who had undergone HbeAg or HbsAg seroconversion were not offered open-label treatment, but were to return for study visits through week 240 to evaluate the durability of seroconversion.

4. Rationale for Doses Used in the Trial

The doses for the three groups were selected based on PK data obtained from study GS-02-517. In a 70-kg adult, the approved dose of 10 mg/day correlates to 0.14 mg/kg. Historical adult exposures based on this dose are Cmax = 18.36 ng/mL and AUC_{inf} = 230.34 ng*hr/mL.

In children ages 2 to 6, a dose of 0.3 mg/kg/day produced exposures of Cmax = 26.93 ng/mL and AUC_{inf} = 224.1 ng*hr/mL. This closely matched the adult exposures and was thus selected as the study dose for this group. However, in children ages 7 to <12, a dose of 0.3 mg/kg/day gave exposures of 30.89 ng/mL and 273.29 ng*hr/mL, while the 0.14 mg/kg dose gave exposures of 14.12 ng/mL and 128.5 ng*hr/mL. Estimates of an appropriate dose from a noncompartmental model resulted in a dose selection of 0.25 mg/kg for this group. In the 12 to <18 years group, the

rate and extent of adefovir exposure from the 10-mg dose (Cmax = 22.75 ng/mL, AUC_{inf} = 237.3 ng*hr/mL) was similar to adult exposures, so the 10-mg dose was selected. For all age groups, the daily dose was not to exceed 10 mg.

5. Drugs Used in the Trial

The currently approved 10-mg tablet and the re-formulated oral suspension formulation were used in this study. The original oral suspension was re-formulated to improve its palatability. The new formulation was also shown to be bioequivalent to the 10-mg tablet in adults (study GS-02-536).

6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood and urine samples were collected to assess adefovir drug levels at pre-dose, 4, 8, 12, 24, 36, and 44 weeks post-dose. The time points for blood samples were: 0, 0.25 (0-0.5), 0.75 (0.5-1), 1.5 (1-2), 2.5 (2-3), 3.5 (3-4), 4.5 (4-5), 6 (5-7), 8 (7-9), 10 (9-11), 12 (11-13), 14 (13-15), 16 (15-17), 18 (17-19), 20 (19-21), 22 (21-23), and 23.5 (23-24) hours post-dose. Because only one randomly timed plasma sample was collected from each subject at each visit, adefovir concentrations were pooled by age group for the PK analysis.

Bioanalysis

Analytical services were provided by Gilead Sciences Bioanalytical Laboratory (Durham, NC) using a validated LC/MS/MS assay. A linear calibration curve was obtained for standard concentrations between 1.00 ng/mL to 200 ng/mL, with an LLOQ of 1.00 ng/mL. Accuracy ranged from 93.7 to 104.8% of nominal, while precision (%RSD) ranged from 3.89 to 11.36%. QC concentrations were 3.0, 75.0, and 150 ng/mL. A total of 1370 human plasma samples were analyzed in 14 batches. All batches met the acceptance criteria.

Pharmacokinetic Assessments

The pharmacokinetic analysis set includes all subjects who had at least one measurable plasma adefovir concentration. Primary PK parameters for adefovir were assessed by the application of a non-linear curve fitting method (WinNonlin) using one-compartment and noncompartmental methods. The linear/log trapezoidal method was used in combination with Model 200. The one-compartment model with first-order input and elimination rate constants with no lag time was used.

Statistical Analysis

The PK statistical analysis included all subjects who received study drug and participated in at least one PK study visit and who had a PK profile deemed evaluable by Gilead.

7. Results

Adefovir exposures were comparable between all three age groups. Additionally, these exposures also matched the adult exposures obtained study GS-00-472. In GS-00-472, the median Cmax in adult CHB patients was 16.7 ng/mL (range, 9.2-38.7) and the steady-state AUC_{0-24} was 185.6 ng*h/mL (range, 124.3−367.0). In the current study, based on the one-compartment model and median concentration data, the predicted Cmax values of the age groups in the current study ranged from 16.01 to 22.26 ng/mL, and the predicted AUC_{0-24} values ranged from 201.24 to 239.77 ng*h/mL.

Figure 4

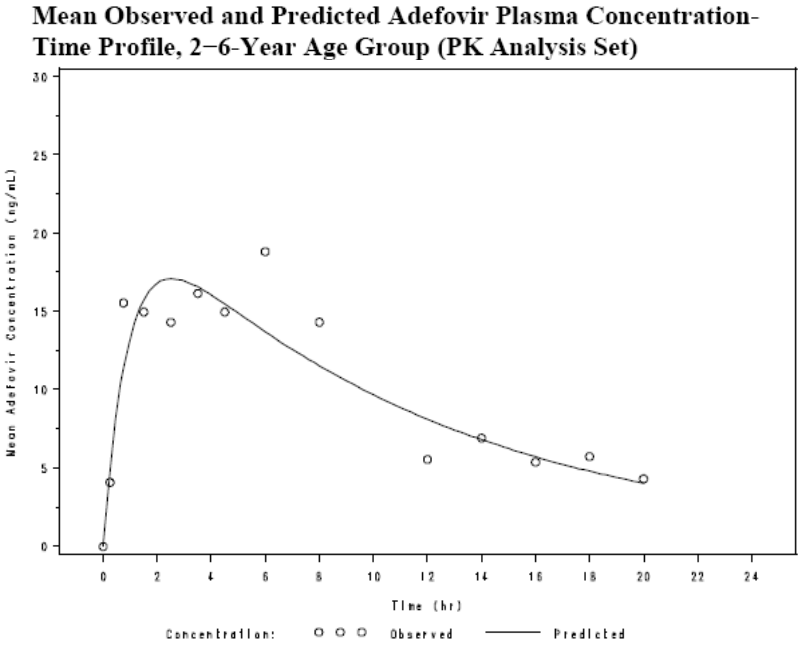


Figure 5

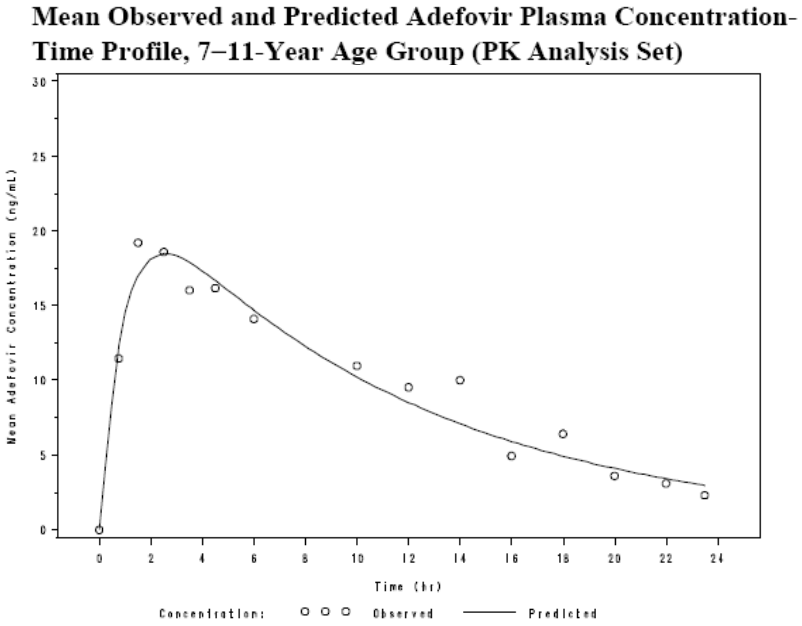


Figure 6

Mean Observed and Predicted Adefovir Plasma Concentration-Time Profile, 12–17-Year Age Group (PK Analysis Set)

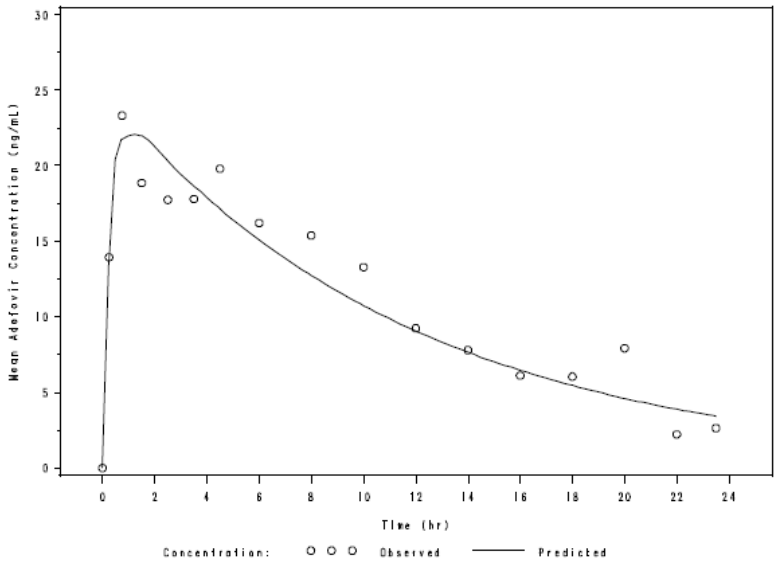


Table 6

Pharmacokinetic Parameter [a] Model	2–6 Years [b]	7–11 Years [b]	12–17 Years [b]
AUC_{0-24} (ng•h/mL)			
One-Compartment Model			
Mean	210.37	222.09	248.76
Median	201.24	228.21	239.77
Noncompartmental Model			
Mean	218.96	227.91	261.87
Median	216.77	233.43	252.06
C_{max} (ng/mL)			
One-Compartment Model			
Mean	17.09	18.47	21.96
Median	16.01	19.54	22.26
Noncompartmental Model			
Mean	18.83	19.21	23.33
Median	18.75	20.55	22.50
T_{max} (h)			
One-Compartment Model			
Mean	2.50	2.50	1.50
Median	2.50	2.50	1.50
Noncompartmental Model			
Mean	6.00	1.50	0.75
Median	6.00	2.50	0.75
$T_{1/2}$ (h)			
One-Compartment Model			
Mean	7.92	7.58	8.17
Median	8.25	7.62	7.50
Noncompartmental Model			
Mean	10.20	5.35	5.36
Median	13.11	5.35	5.15

ADV = adefovir dipivoxil, AUC_{0-24} = area under the plasma concentration versus time curve from Time 0 to 24 hours after the dose, C_{max} = maximum observed concentration of drug in plasma, $T_{½}$ = estimate of the terminal elimination half-life of drug in plasma, T_{max} = time to maximum observed concentration of drug in plasma

a Adefovir plasma pharmacokinetic parameters were estimated based on the pooled adefovir plasma concentrations for each age group (Section 5.7.2.6.5).

b Age at first dose of study treatment; ranges are inclusive (i.e., 2 to < 7 years; ≥ 7 to < 12 years; ≥ 12 to < 18 years).

In general, adefovir PK parameters predicted by the one-compartment model were in good agreement with results form the noncompartmental model.

8. Conclusions

After 48 weeks of adefovir dipivoxil treatment, antiviral efficacy in HBeAg+ CHB patients in the 12−17-year age group was similar to that observed in a study in treatment-naive adults with HBeAg+ CHB (Study GS-98-437). Adefovir dipivoxil was less effective in subjects in the 7−11-year age group, and effectiveness was further reduced in subjects in the 2−6-year age group

despite adefovir concentrations similar to adults in all three age groups. Although adefovir dipivoxil had some antiviral effect in subjects in the two lower age groups, the effect was insufficient to suppress HBV DNA below 1000 copies/mL in most of the subjects in this age range.

Adefovir plasma concentrations were comparable in all three pediatric age groups, and each age group achieved adefovir concentrations in the target range (adefovir plasma concentrations in adult CHB patients with established safety and efficacy profiles).

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