CLINICAL REVIEW

Application Number	21-449
Submission Number	SE5-011
Submission Code	N
Letter Date	25 June 2007
Stamp Date	27 June 2007
PDUFA Goal Date	24 December 2007
Reviewer Name	Yodit Belew, M.D.
Review Completion Date	12 December, 2007
Established Name	Adefovir Dipivoxil
Trade Name	Hepsera® Tablet
Therapeutic Class	Anti-Hepatitis B (Nucleotide Analog)
Applicant	Gilead Sciences Inc.
Priority Designation	P
Formulation	Tablet
Dosing Regimen	10 mg PO Once Daily
Indication	Treatment of Chronic Hepatitis B Infection
Intended Population	Pediatric patients (12- <18 years old)

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Recommendation on Regulatory Action

This NDA (NDA 22-449 SE5-011) seeking approval of Hepsera® (adefovir dipivoxil) (adefovir) (ADV) tablets for use in pediatric patients 12 - <18 years of age, should be approved. Based on the data submitted, Hepsera® should not be approved for use in patients <12 years of age.

Gilead Sciences (the Applicant) submitted adequate data characterizing the pharmacokinetics of Hepsera® tablets in pediatric patients that support a dose of adefovir 10 mg PO once daily for ages 12 - <18 years old. This conclusion is reached following review of the application containing safety and antiviral activity data from 173 pediatric patients aged 2 to <18 years with chronic hepatitis B infection treated with Hepsera® tablets for at least 48 and up to 144 weeks. The data demonstrate comparable exposures (e.g., AUC) in pediatric patients compared to adult patients, comparable exposures (e.g., AUC) between the tablet and suspension formulations, as well as comparable exposures (e.g., AUC) among the three pediatric age groups (2- <7, 7- <12, 12- <18). Overall, the proportion of subjects with <1000 copies/mL of HBV DNA plus normalization of ALT (primary efficacy endpoint) was higher for the adefovir treated group when compared to the placebo group (20% vs. 2%, p<0.001). In subjects who received adefovir tablets, all of whom were in the older age group (12- <18 years of age), the response to treatment was statistically significant (23% vs. 0, p= 0.007) when compared to placebo. Subjects in the younger age groups (2-<7 years old and 7- <12 years old) all received the suspension formulation. Despite the formulation having no chemistry or pharmacokinetics issues, the response in these age groups (2 - < 12 years), although numerically higher that the placebo treated group, the difference was not statistically significant (age 2- <12 years: 17% vs. 3%, p =0.089; age 2-<7years: 17% vs. 8%, p =.634; age 7-<12 years: 17% vs. 0%, p= .083). It should be emphasized that the study was not designed (powered) to assess efficacy among the different age groups. The number of subjects in the two younger age groups was smaller than in the oldest cohort.

In summary, treatment with adefovir was shown to have benefit as the proportion of subjects who met the primary efficacy endpoint was higher in the adefovir treated group when compared to placebo. When analyses was preformed by age, a statistically significant difference was seen only in the 12-<18 years old age group. Adefovir does not appear to have very potent activity as a hepatitis B drug in pediatric patients. Nonetheless, given that there are only two approved therapies for use in the pediatric population for the treatment of hepatitis B, approval of adefovir (for 12-<18 years of age), will be of benefit given the limited choices of options that are available.

Based on the results from the analyses by age,

however, pertinent information on patients < 12 years of age will be included in relevant sections of the label as recommended by the Best

Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) reauthorizations.

Recommendation on Postmarketing Actions

Risk Management Activity

Hepsera® tablets have been marketed in the US since 2002 with a patient package insert. No post-marketing concerns have emerged. As such, no new risk management activity is required.

Required Phase 4 Commitments

- The Applicant has conducted a pediatric study in patients 2 to < 18 years of age to address the requirements of the Pediatric Written Request (PWR) as well as one of their Post Marketing Commitments (PMC). This submission fulfills the PMC for this age group. Because the amended study design limited follow-up data, the Applicant was not able to collect all data stipulated in the PWR. As such, the Applicant will not be seeking Exclusivity to be granted. The Applicant has submitted a safety update which has been reviewed and included in this review document.
- The Review Team recommends releasing the Applicant from their PMC to evaluate Hepsera in patients from birth to 2 years of age.

Summary of Clinical Findings

Brief Overview of Clinical Program

The clinical program to support approval of Hepsera® tablets in patients 12- <18 years of age included a single, randomized, double-blind, placebo-controlled, parallel-group study in which 173 pediatric patients with CHB infection received adefovir. The study was randomized 2:1 with 58 subjects receiving placebo and 115 subjects receiving adefovir. The subjects were divided into 3 cohorts based on age: 2-<7 years old (cohort 1), 7-<12 years old (cohort 2), and 12- <18 years old (cohort 3). All subjects in cohort 3 received tablet formulation (10mg PO once daily) and all subjects in cohorts 1 and 2 received an investigational suspension formulation (0.3 mg/kg/day cohort 1, 0.25 mg/kg/day cohort 2). In addition, data were submitted from the clinical pharmacology studies that assessed bioavailability, pharmacokinetics, and dose-ranging of adefovir administered as oral suspension and tablet.

Efficacy

Overall, 23 (20%) of pediatric subjects treated with adefovir vs. 1(2%) of placebo treated subjects achieved the primary endpoint of HBV DNA level <1000 and normalization of ALT by week 48 ($p < 0.001$). Across all study participants by age, 4(17%) vs. 1(8%) ($p = 0.634$) of cohort 1, 6(17%) vs. 1(0%) ($p = 0.083$) of cohort 2, and 13(23%) vs. 0 (0%) ($p = 0.007$) of cohort 3 achieved the primary efficacy endpoint by week 48. It should be mentioned that the study was not designed or powered to study treatment effect based on age group. Therefore, the less

significant treatment effect (when compared to placebo) seen with individual cohorts should be interpreted with caution.

There also appears to be a significant difference in efficacy outcome based on formulation of adefovir (tablet or oral suspension) used [suspension group: adefovir (17%) vs. placebo (3%), p = 0.089; tablet group: adefovir (23%) vs. placebo (0%), p = 0.007]. This difference follows the age groups, as those older than 12 years of age received exclusively the tablet (adult) formulation while those younger than 12 years of age all received the suspension formulation. However, it must be emphasized that this apparent difference was not due to the formulation itself (i.e. concerns with the suspension formulation). No chemistry or pharmacology issues were identified.

The mechanism of action of adefovir is inhibition of HBV DNA polymerase (reverse transcriptase). Because its target is hepatitis B virus, one would expect adefovir to work similarly in adults and children of varying ages. The differences in response observed among the age groups may be due to different manifestation of chronic HBV infection in children, i.e. immunotolerance- defined as normal or near normal serum ALT, very high serum HBV DNA level and persistent HBsAg and HBeAg positivity.

Immunotolerance is a phenomenon unique to pediatric subjects especially those acquiring infection early in life and is not seen in adults with CHB infection. Because of immunotolerance, treatment of CHB in children has been difficult. Unlike in the adults, there is no established treatment guideline for CHB in children. As such, it is difficult to find a consistent approach among pediatric hepatologists as to when to initiate treatment. However, there is a one recommendation that most hepatologists adhere to- that one should delay therapy until there is persistent elevation in ALT.

When patients in this adefovir study were evaluated based on baseline ALT (i.e. 2x ULN) (N=102), the overall response was 21% adefovir vs. 0% placebo (p = 0.002). The proportion of subjects with HBV DNA <1000 copies/mL plus normalization of ALT among the 3 adefovir treated cohorts is similar - 23% for cohorts 1 and 2, 20% for cohort 3. However, the treatment responses in each group, when compared to the respective placebo groups, were not statistically significant. This may be related to the smaller number of subjects per cohort in the subgroup analyses.

None of the additional subgroup analyses performed (efficacy outcome by baseline HBV DNA level, efficacy outcome by HBeAg loss or seroconversion by Week 48) showed a statistically significant treatment difference according to age group, when comparing adefovir to placebo.

Safety

Hepsera® is an approved product with a well characterized safety profile. Nephrotoxicity has been associated with long term treatment with adefovir. Treatment-related renal adverse events (increase in creatinine, decrease in creatinine clearance) were not increased in frequency in

pediatric patients compared to adult patients. Infection and Infestations and Anorexia were more commonly observed in the pediatric studies.

The common adverse events related to adefovir in the adult studies included: asthenia, headache, abdominal pain, nausea, flatulence, diarrhea, dyspepsia. Grade 3-4 laboratory abnormalities reported in ≥ 1% of adefovir treated patients included: increased ALT and AST (>5 x ULN) in 20% and 8%, respectively, hematuria (3+) in 11%, elevated creatine kinase (>4 x ULN) 4%, increased amylase (>2x ULN) 4%, and glycosuria (>3+) in 1%.

The most common adverse events reported in the pediatric study were abdominal pain, cough, headache, nasopharyngitis, pharyngitis, pyrexia, and upper respiratory tract infection.

Renal adverse events were reported in one adefovir treated subject and 2 placebo treated subjects. An adolescent male on adefovir treatment group had a Grade 1 proteinuria which resolved without treatment interruption or interventions. Serum creatinine and creatinine clearance remained within normal limits. No subject had confirmed increase in serum creatinine ≥ 0.5mg/dL. No subject had confirmed phosphorus < 2.0mg/dL.

Four adefovir treated subjects reported hepatic adverse events: ALT increased (3 subjects), and hepatomegaly (1 subject). One of the subjects with enzyme elevation had a Grade 3 SAE and event was considered treatment related. All hepatic AEs in adefovir treated subjects resolved without intervention during continued treatment. The events in the placebo treated subjects were hepatitis (2 subjects) and ALT increased (1 subject). No subject showed evidence of hepatic decompensation.

Dosing Regimen and Administration

Hepsera® (12- < 18 years old): The proposed recommendation of adefovir 10 mg tablet PO daily in patients 12 to 17 years of age, inclusive is based on results from Study GS-US-103-0518. In this study, 12 to <18 year old subjects received adefovir 10 mg PO QD. Plasma adefovir exposures were consistent with the historical adult population receiving adefovir 10 mg PO QD, with ~14% higher plasma AUC (0-24) and similar Cmax.

Hepsera® (2- <12 years old): The Applicant does not seek approval in pediatric patients younger than 12 years of age.

Clinical data for this age group was submitted and reviewed. Pertinent information will be included in the label (Adverse Reactions, Use in Special Populations, Clinical Studies and Clinical Pharmacology sections).

Drug-Drug Interactions

Drug-drug interaction studies were conducted during development of the tablet formulation of adefovir. Relevant drug-drug interaction information, including recommendations for dose adjustments of adefovir or other agents, is already included in the Hepsera® tablet label.

Special Populations

In addition to pediatric patients, Hepsera® oral suspension was studied for use in adults who need dose adjustment due to renal failure or insufficiency (NDA 21-449, submitted on January 10, 2006). This data was reviewed by Dr. Charlene Brown. Using subjects with renal impairment, the study compared dose adjustments: keeping once daily dosing but changing the total dosage (using suspension formulation) vs. keeping the 10mg QD dosing but decreasing the frequency of administration (using tablet formulation). The conclusion of the study was that there was no added benefit gained from the suspension formulation. Please see Dr. Brown's review for further detail.

2. INTRODUCTION AND BACKGROUND

The development of hepatitis B vaccine has significantly changed the incidence of CHB in children and adolescents. However, HBV infection continues to be a global health problem, including in the United States. Most new childhood infections in the U.S. are found in populations where either the children or their parents are immigrants from highly endemic places such as Africa and the Far East. Children are born to immigrant women who are infected, or children acquire HBV by horizontal transmission within these households, including households with intravenous drug user (1). It is helpful to subdivide CHB infection in children based on time of infection acquisition (perinatal vs. other modes of transmissions). Perinatal transmission accounts for the largest group (~50%) of new pediatric infection (1). The likelihood of developing CHB infection in children is inversely proportional to the age of acquisition. CHB develops in 90% of infants vertically infected, 25-50% in children infected between ages 1-5 years, and 6-10% of older children(1). Children who have perinatally acquired HBV infection usually have normal or near normal serum ALT, very high serum HBV DNA level and persistent HBsAg and HBeAg positivity (also known as an immunotolerant phase)(2). This phase lasts for years, into late childhood, adolescence or even adulthood. Spontaneous HBeAg seroconversion rates are low for children with perinatal acquisition (i.e. ~2% per year in children less than 3, and 4-5% per year in children greater than 3 years) (2). HBeAg seroconversion rate is higher in those infected after the perinatal period; a European longitudinal studies of children with horizontally acquired CHB infection documented that 70-80% seroconverted over a period of 1-20 years (2).

Most children with CHB grow and develop normally without significant clinical manifestations. In some, the only presenting symptom is nephritic syndrome (secondary to membranous glomerulonephritis) (1). Inflammatory changes are often mild in children but fibrosis may be significant. Hepatocellular carcinoma (HCC) has been reported in children and usually occurs when there is a rapid progression from hepatitis to cirrhosis (1).

There are limited long-term studies of HBV starting in childhood. Prognosis for children with CHB is often derived based on cross-sectional Southeast Asian data from adult cohorts followed in tertiary care centers (2). The lifetime risk of developing HCC is 25%, based on these adult studies. This estimate is not generated from longitudinal studies of HBV infection first diagnosed in childhood. A study by Chang prospectively analyzed the course of 415 children with CHB for

an average of 8 years. Only two children developed cirrhosis, one of whom also developed HCC (2). A long-term study of 174 children in Montreal showed no cases of cirrhosis or HCC (2). Study by Tenyear from the United Kingdom showed no cases of cirrhosis or HCC after a follow up of 73 children (2). At the current time, there are not adequate numbers of pediatric patients with long term follow-up to give an accurate assessment of lifelong risks and predictors of morbidity and mortality in children with CHB (2).

The goals of antiviral therapy in CHB infection include cessation or decrease in viral replication, normalization of aminotransferase and liver histopathology and to ultimately prevent morbidity and mortality associated with cirrhosis and HCC (1).

There are numerous challenges associated with treating children with CHB infection. First, neither of the medications currently licensed in the U.S. were shown to fulfill treatment goals for children (1,2). There is also the concern of long-term safety and efficacy of nucleoside analogs when used in children. Second the disease process in children makes it difficult to identify patients who may benefit from treatment. For example, spontaneous HBeAg seroconversion occurs during childhood. In addition, there is the issue of immunotolerance in children where treatment with nucleoside analogs during this phase is of limited benefit. There is a general consensus among pediatric hepatologists that treatment might be considered for children with biochemically and histologically active disease who may be at higher risk of develop cirrhosis during childhood. However identifying these patients may be difficult since these findings are common in children who are undergoing spontaneous HBeAg seroconversion. Active disease in this setting for more than 6 months may be an indication to consider treatment (2).

Therefore, it is critical that only those who will have benefited from therapy are selected for treatment. They should at minimum: have evidence of CHB infection (detectable serum HBsAg for at least 6 months, and HBeAg and/or detectable HBV DNA). They should also have consistently abnormal ALT values as these are the children who will most likely respond to treatment. For example, it has been shown that although there is significant difference in treatment (interferon alpha) response between Western and Asian children (20-58% vs. 8-17%, respectively), if baseline ALT values are elevated, treatment response rates were similar (22% vs. 26%, respectively) (1). Variables associated with higher likelihood of response with interferon alpha therapy have been shown to include ALT $\geq$ 2x ULN, female gender, low level of HBV DNA, younger age, active inflammation on liver biopsy (1).

A randomized, double blind, placebo-controlled 52 week long trial using lamivudine was performed in 2002. All children were HBsAg positive for at least 6 months, were positive for HBeAg, had detectable serum HBV DNA, ALT >1.3 ULN but less than 500 IU/L and evidence of inflammation on liver biopsy. Of note, an older generation of HBV DNA assay, less sensitive than the one employed today, was used for this study. The primary endpoint, clearance of HBeAg and HBV DNA at 52 weeks, occurred in 23% of treated children (vs. 13% placebo). In those with baseline ALT $\geq$ 2x ULN, response rate was 35%. Elevated baseline ALT was associated with higher likelihood of response to treatment.

Product Information

Adefovir dipivoxil (Hepsera®, adefovir) is a nucleotide analogue approved for treatment of adults with chronic hepatitis B infection. The current application provides data to support the extension of treatment in pediatric patients (ages 12 to < 18 years).

Adefovir dipivoxil is a diester prodrug of adefovir, an acyclic nucleotide analog of adenosine monophosphate. It is phosphorylated to adefovir diphosphate by cellular kinase. Adefovir diphosphate inhibits DNA polymerase (reverse trascriptase) and causes DNA chain termination after its incorporation into viral DNA.

Currently Available Treatment for Indications

In addition to adefovir, there are currently 4 approved drug moieties available in the US for the treatment of CHB infection in adults: Interferon-alpha (Intron A®, Pegasys®), lamivudine (Epivir-HBV®), entecavir (Baraclude®), and telbivudine (Tyzeka®). Only Intron A® and lamivudine have been studied and approved for use in children in the United States.

Presubmission Regulatory Activity

Adefovir was initially developed as a 10 mg tablet, and approved in the United States in 2002 for the treatment of adults with CHB infection (NDA 21-449).

On 12 April 2002, a Pediatric Written Request for adefovir (with subsequent amendments on 02 July 2002, and 07 May 2004) was issued requesting pharmacokinetic, antiviral activity and safety data in 100-150 pediatric patients with CHB infection who have received the proposed dose(s) for marketing for at least 48 weeks with safety and durability of response to adefovir evaluated during the second 48 weeks of study. Long term safety follow-up for up to 5 years with at least 50% of subjects completing 3 years of follow up by January of 2008 was also requested.

The submission of this application is intended to fulfill the postmarketing commitment specified in the NDA letter of approval (NDA 21-449) for the treatment of CHB infection in adults (dated 20 September 2002). The PMC required that a study be conducted "for the treatment of chronic hepatitis B infection in pediatric subjects from 2 to 17 years of age. Conduct a pediatric safety and efficacy study of adefovir dipivoxil with efficacy based on the results of a variety of virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks."

A study evaluating the comparative bioavailability of the developed oral suspension formulation and the commercial tablet dosage form demonstrated equivalence between the two formulations. Food effect on the tablet formulation was evaluated with the initial (original) NDA submission. The tablet was found to exhibit high oral bioavailability and food did not have effect on its pharmacokinetics. Food effect was not tested on the suspension formulation "because of the

good oral bioavailability observed with the tablet formulation and the lack of a food effect on tablet bioavailability."

Other Relevant Background Information

Although the currently submitted data meets the postmarketing commitment specified in the NDA letter of approval, it falls short of fulfilling the requirements of the Pediatric Written Request which would have led to granting exclusivity.

Specifically, Amendment 2 to Study 518 recommends that patients discontinue treatment with adefovir at week 96 of study in case their HBV DNA values are ≥ 1000 copies/mL as observed at two consecutive visits (12 weeks apart). Additionally, Amendment 2 allows for the addition of lamivudine to treatment with adefovir in patients who have had prior treatment with lamivudine; and in case patients for whom lamivudine was added continue to have HBV DNA values ≥ 1000 copies/mL as observed at two consecutive visits, it is recommended that treatment for these patients be discontinued.

The implementation of Amendment 2 has affected the ability to follow *at least 50%* of the patients from the original treatment group for 3 years by January of 2008. Gilead proposed that

Additional significant background information to this sNDA submission is that the Applicant did not submit (with this sNDA) the CMC data for the suspension formulation. The decision not to submit was based on their analyses of the efficacy results at the end of the blinded treatment period (Week 48). They concluded that the difference in treatment response between adefovir and placebo in younger age groups (2-<12 years old) was not statistically significant. All subjects <12 years of age received the suspension formulation. Based on this result, the

the effectiveness of adefovir appears to delineate by the formulation type and there is no overlap of formulation usage in the older age group in whom the drug did appear to have benefit.
The Division requested that all CMC data relating to the suspension formulation be submitted in order to establish that the effectiveness of the drug was not diminished due to CMC issues such as stability of the suspension formulation. The Applicant subsequently submitted the requested CMC information and review of the data indicated that there was no issue with the formulation.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC and Microbiology

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Allan Fenselau's review. In brief, the conclusion was that the CMC information found in the amendment to this submission as well as in IND 52,182 and its relevant amendments is sufficient to conclude that no CMC issues are associated with the suspension formulations employed in the clinical studies that failed to exhibit comparable effectiveness when compared to the tablet formulation. For a discussion of Microbiology, please see Dr. Lalji Mishra's review.

Animal Pharmacology/Toxicology

All animal pharmacology/toxicology studies were conducted during development of Hepsera® tablet. There were no issues identified that would lead to a conclusion that Hepsera® would not be safe to administer to pediatric patients older than 2 years of age. Please refer to NDA 21-449 for a more detailed review.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

The clinical data submitted in this application was derived from a single randomized, placebo-controlled, double-blind study conducted by the Applicant as well as number of phase 1/2 clinical pharmacology studies.

Tables of Clinical Studies

Tables 1 and 2 represent an overview of the pivotal pediatric clinical studies submitted to support the safety and efficacy of Hepsera® tablet and suspension formulations.

Table 1: Pivotal Pediatric Hepsera® Studies

Clinical Study No	Type of Study	Type of Subject	ADV oral suspension Formulation
GS-02-515	Phase 1 single-dose crossover study evaluating PK of ADV suspension and marketed tablet (10-mg dose)	Healthy adults	suspension Formulation A
GS-02-517 [a]	Phase 1/2 PK study	Pediatric CHB patients 2− < 18 years	suspension Formulation A
GS-02-536	Phase 1 single-dose crossover study evaluating PK of ADV suspension and marketed tablet (10-mg dose)	Healthy adults	suspension Formulation B
GS-US-103-0518 [b]	Phase 3 placebo-controlled efficacy and safety study	Pediatric CHB patients 2− <18 years	Suspension Formulation B

a All subjects received the suspension formulation.
b Subjects 2−11 years old received the suspension formulation; subjects 12−17 years old received the tablet formulation.

The bioequivalence of adefovir suspension Formulation A and the marketed 10-mg tablet was demonstrated in Study GS-02-515. A pharmacokinetics study (GS-02-517) using suspension Formulation A was then conducted in CHB infected patients 2−17 years old to identify the doses to be evaluated for efficacy and safety in pediatric patients. After completion of GS-02-517, changes were made in the flavoring of the oral suspension formulation to improve its palatability. The resulting formulation, suspension Formulation B, was then evaluated in Study GS-02-536 to establish its bioequivalence to the marketed 10-mg tablet. After bioequivalence of the formulations was established, the Phase 3 efficacy and safety study in pediatric CHB patients 2− <18 years old was initiated (GS-US-103-0518).

Table 2: Phase 3 Clinical Study

Protocol No. Countries	Dates	Design Population	Treatment Regimens	No. Patients Treated Ages
GS-US-103-0518 26 study centers United States, Poland, Germany, United Kingdom, Belgium, Spain	Start date: 17 May, 2004 First Subject randomized: 21 June 2004 Last Subject Randomized: 08 June 2005 Last Subject Observation for this Report: 04 May 2006 Database Lock for this Report: 28 July 2006 Unblinding: 01 August 2006	Randomized, placebo-controlled, double-blind, in pediatric subjects 2-<18 years with CHB	ADV: 2-<7 y: 0.3mg/kg/day PO QD 7-<12 y: 0.25 mg/kg/day PO QD 12-<18y: 10 mg PO QD PLB: Matching dosing regimen	2-<7 Years: N= 23 ADV N= 12 PLB 7- <12 Years: N= 36 ADV N= 19 PLB 12- <18 Years: N= 56 ADV N= 27 PLB Total: N= 115 ADV N= 58 PLB

Review Strategy

Study GS-US-103-0518 was reviewed in its entirety. Two data sets were submitted. The first contained the blinded 48 week data. This data set included CSR (safety, and efficacy) and CRFs. Data from the open label phase of the study (weeks 49-144) was submitted as a follow-up (120 day) safety report and included safety data up to week 144. In addition studies GS-02-515, GS-02-517, and GS-02-536 were reviewed by the Clinical Pharmacology team for bioequivalence and pharmacokinetic data.

Data Quality and Integrity

The submitted data appears to be with good quality and integrity. There was no issue in accessing any of the data sets.

Compliance with Good Clinical Practices

It appears that the clinical trial was conducted in compliance with Good Clinical Practices and in accordance with acceptable ethical standards.

5. CLINICAL PHARMACOLOGY

Pharmacokinetics

Bioequivalence and dose ranging in pediatric patients were assessed in previous clinical pharmacology studies (GS-02-515, GS-02-517, and GS-02-536). Impact of food on pharmacokinetics was assessed with the initial submission of the NDA. Please refer to the Clinical Pharmacology Review by Dr. Shirley Lu. In summary, the clinical pharmacology and biopharmaceutics information pertaining to similarity in exposures between the suspension and tablet formulation is acceptable. In addition, the exposures produced by 10mg tablets in patients 12 - <18 years of age were similar to those found to be safe and effective in adults. The exposures of adefovir demonstrated in patients 2 - <12 years of age using adefovir suspension were also similar and did not account for lack of efficacy in the younger age groups.

Pharmacodynamics

No Pharmacodynamics studies were conducted for this application.

Exposure-Response Relationships

Not applicable

6. REVIEW OF EFFICACY

Indication

The proposed indication is "for the treatment of chronic hepatitis B in adults and in adolescents aged ≥12 to <18 years with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease."

Methods

Study GS-US-103-0518 was reviewed in its entirety. The CSR provide by the Applicant was reviewed. In addition, this reviewer performed an independent analysis of the data using JMP. Further, the efficacy result was independently analyzed and reviewed by Dr. Karen Qi (Biometrics Statistical Reviwer).

General Discussion of Endpoints

As mentioned previously, there are only two therapies for CHB infection in children that are approved by the FDA. Only lamivudine precedes adefovir as an anti-viral (HBV) drug. When adefovir was studied in adults with CHB infection, the primary efficacy endpoint was histological improvement at week 48.

Histology was not elected for assessment of primary endpoint for this pediatric study because it is not used as a standard of care in pediatrics for assessment of treatment response. The applicant and the FDA agreed that efficacy would be measured using a composite endpoint that included a combination of normalization of ALT and decline in HBV DNA (by PCR). The proportion of patients who become HBeAg negative during the study period was a secondary endpoint. The Applicant's primary endpoints were as follows: "The proportion of subjects with serum HBV DNA < 1000 copies/mL and normal ALT at Week 48.".

Study Design

A single, randomized, placebo-controlled, double-blind study provided the basis for the evaluation of efficacy of adefovir in patients 2 to <18 years of age.

GS-US-103-0518 is a randomized, placebo-controlled, double-blind study of a once daily dose of adefovir tablet or oral suspension in pediatric patients with CHB infection. The primary study objective is: 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. The secondary objectives are: (1) 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, (2) to evaluate the proportion of children and adolescents who experience HBeAg and HBsAg seroconversion following 48 weeks of treatment with adefovir dipivoxil or Placebo, (3) to evaluate the development of conserved site mutations associated with resistance to adefovir dipivoxil, (4) 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.

The study was started on May 17, 2004 and the first subject was randomized on June 21, 2004. The last subject observed for this blinded period report was on May 4, 2006. The database was locked on July 28, 2006 and unblinding occurred on August 1, 2006. One hundred and seventy three subjects were enrolled in the study. The study was conducted at 26 sites: United States (12), Poland (5), Germany (4), United Kingdom (3), Belgium (1), and Spain (1).

The study has two major periods: Week 1-48 and Week 48-144. The first period is the randomized, placebo-controlled, double blind phase of the study. At the Week-44 visit, subjects were evaluated for HBeAg or HBsAg seroconversion. The results of these tests were sent to an unblinded statistician at the CRO who identified placebo-treated subjects who had undergone seroconversions, and investigators were then notified that those subjects were not eligible for the open-label adefovir treatment starting in Week 49. All subjects in the adefovir group and those subjects in the placebo group who did not exhibit seroconversion at Week 44 were offered the

opportunity to start open-label adefovir treatment in Week 49. Subjects in the placebo group who exhibited seroconversion at Week 44 were to return for study visits through Week 144 to evaluate the durability of seroconversion.

There were 2 amendments to the study protocol. Important points from these amendments are briefly outlined:

Amendment 1 (12 August 2004):

- Revision of the definition of a severe hepatic flare; instructions were added to ensure that investigators immediately notified the Sponsor of severe hepatic flares; protocol was revised to indicate that severe hepatic flares were to be considered a serious medical event that must be reported as an SAE within 24 hours.
- The inclusion criterion for serum ALT concentration was changed from ≥ 1.2 times upper limit of the normal range (ULN) to ≥ 1.5 × ULN

Amendment 2 (07 July 2006):

- Subjects with a serum HBV DNA concentration ≥ 1000 copies/mL at two consecutive study visits at or after Week 96 should have lamivudine added to the adefovir regimen. If the HBV DNA concentration remains ≥ 1000 copies/mL at two consecutive study visits after the addition of lamivudine, treatment should be discontinued and have the subject return every 4 weeks for 16 weeks of post-treatment evaluations.
- The off-treatment follow-up period originally planned in Weeks 144 to 240 was changed. Instead, subjects who do not have persistent viremia (i.e., those who had serum HBV DNA < 1000 copies/mL) are to be allowed to continue on open-label adefovir dipivoxil treatment through Week 240, provided they are tolerating treatment and have not undergone confirmed HBeAg or HBsAg seroconversion.

Proposed protocol changes by the Applicant at the time of the sNDA submission:

M.O. Comments: Due to Amendment 2 (see above), evaluation for safety (and durability) of adefovir for up to 5 years with at least 50% of subjects completing 3 years of follow up by January 2008, was not possible. At week 96, significant number of subjects either withdrew or had additional therapy (lamivudine) added to their regimen. The Applicant has submitted a

safety update on subjects who have received treatment during the second 48 week period (i.e. Week 49-96) and beyond. The last recorded visit for any subject is Week 144.

The major inclusion and exclusion criteria are as follows:
Inclusion:

- Documented CHB (positive HBsAg present for ≥ 6 months prior to randomization); HBsAg must have been positive at the initial screening visit before subjects could be enrolled into the study
- Documented positive HBeAg at screening
- Serum HBV DNA ≥ 1 × 10^5 copies/mL (polymerase chain reaction [PCR] assay) at either the initial or confirmatory screening visits
- Serum ALT levels ≥ 1.5 × ULN at both the initial screening and confirmatory screening visit
- Compensated liver disease
- Adequate renal function defined as creatinine clearance ≥ 80 mL/min.

Exclusion:

- Subjects with a Child-Pugh-Turcotte score > 6
- Received interferon therapy within 6 months prior to the initial screening visit
- Received lamivudine therapy within 6 months prior to the initial screening visit

Adefovir 10mg tablets were available to subjects who were at least 12 years of age at the start of the study. All subjects younger than 12 years of age received the suspension formulation. Subjects who turned 12 during the study were not allowed to switch to the tablet formulation. Subjects taking the adefovir oral suspension would receive adefovir 0.3mg/kg (up to a maximum daily dose of 10 mg QD) if they are 2- <7, and 0.25mg/kg (up to a maximum daily dose of 10 mg QD) if they are 7- <12 years of age.

Subjects were randomized in a 2:1 ratio to treatment with adefovir or placebo for the first 48 weeks of the study. Randomization was centralized and used an interactive voice-response system (IVRS). Randomization was stratified according to age (2 to < 7 years, ≥ 7 to < 12 years, or ≥ 12 to < 18 years) and prior treatment for CHB (prior therapy or no prior therapy).

Disposition

Of the 293 subjects who were screened, 173 were randomized and treated (115 adefovir, 58 placebo). The first subject was randomized on 21 June 2004, and the last was randomized on 08 June 2005. All placebo-treated subjects completed the 48 weeks of double-blind treatment phase. Ninety seven percent (112/115) of the adefovir treated subjects also completed the double-blind treatment phase. The three subjects who discontinued prematurely were in the 12−17-year adefovir group (group 5): One subject discontinued the study because of AEs (psychiatric AE) and two subjects were withdrawn because of noncompliance (one subject missed visits at Weeks 4, 8, and 12; another subject a female was lost to follow-up after ~7 months of therapy and an unconfirmed pregnancy was also reported). Figure 1 depicts the disposition of all subjects and Table 3 shows disposition by age and treatment group.

Figure 1: Disposition

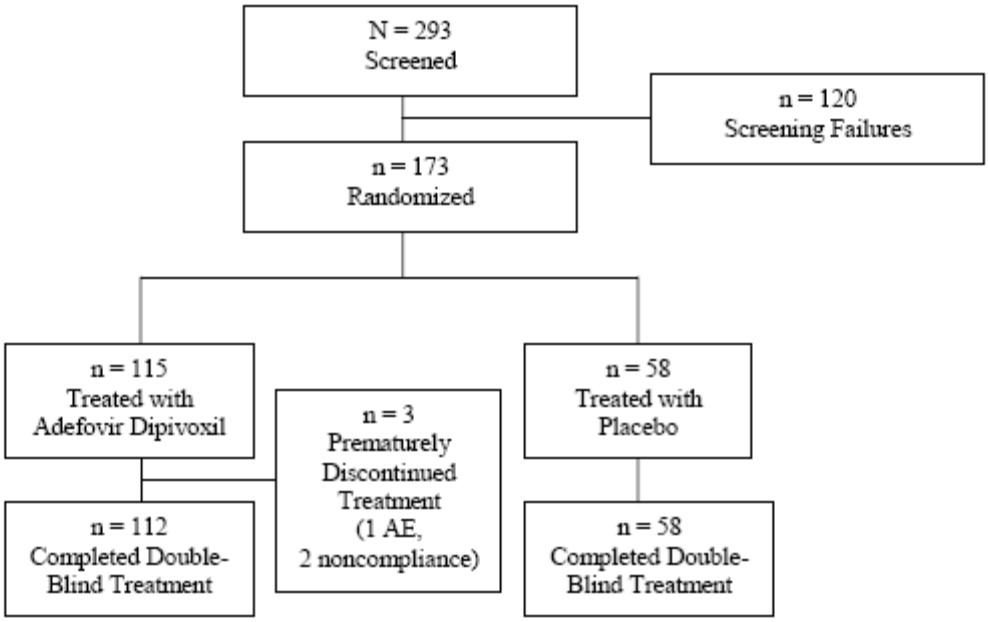

Table 3: Disposition by Age and Treatment Group

Subject Disposition (n, %)	2−6 Years a		7−11 Years a		12−17 Years a		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Treated	23	12	36	19	56	27	115	58
Completed Treatment	23 (100%)	12 (100%)	36 (100%)	19 (100%)	53 (95%)	27 (100%)	112 (97%)	58 (100%)
Discontinued Blinded Treatment Prematurely:	0	0	0	0	3 (5%)	0	3 (3%)	0
Adverse Event	0	0	0	0	1 (2%)	0	1 (< 1%)	0
Noncompliance	0	0	0	0	2 (4%)	0	2 (2%)	0

Protocol Deviation

Screening and baseline ALT values

When the original protocol was submitted, the following were among the inclusion criteria:

- Documented chronic hepatitis B (positive HBsAg present for ≥ 6 months prior to randomization)
- Documented positive HBeAg and negative anti-HBe at screening.
- Serum HBV DNA ≥ 1 x 10^5 copies/mL (PCR assay) at either the initial or confirmatory

screening visit.
- Serum ALT levels ≥ **1.2 x ULN** using an average of the 2 values obtained at the initial screening and confirmatory screening visits.

An amended protocol (Amendment 1 submitted 12 August 2004) revised the inclusion criteria to require serum ALT levels to be **≥1.5 x ULN** at both the initial screening and confirmatory screening visit. With the application of the amended protocol, 34/173 (20%) subjects with either one or both of the screening/confirmatory screening visits did not have serum ALT level ≥ 1.5 ULN). Seventeen subjects had one of the values <1.5 x ULN; another 17 subjects had both values < 1.5 x ULN. Out of these 34 subjects, 19 (56%) had baseline ALT value that was also <1.5 x ULN. Thirty seven (16%) of the total 173 subjects had baseline ALT < 1.5 x ULN. Of those, 20 (74%) subjects had baseline ALT <1.2 x ULN.

M.O. comment: The protocol deviation which allowed enrollment of subjects with ALT <1.5xULN may have had an impact on the study outcome since children with elevated ALT are expected to have response to treatment more than those with normal ALT.

Screening HBsAg
All subjects had documented HBsAg at screening and all were positive.

Screening HBV DNA value
All Subjects had serum HBV DNA ≥ 1 x 10^5 copies/mL (PCR assay) at either the initial or confirmatory screening visit.

Screening HBeAg
All subjects had documented HBeAg at screening and all were positive.

Medication errors:
- Missed dose (>6): in the adefovir arm, 14% (5/36) of subjects in the 7−11-year age group, and 9% (5/56) of subjects in the 12−17-year age group missed > 6 doses. One subject in the 12-17 year old group was withdrawn due to noncompliance.
- Overdose: 3 subjects in the adefovir arm received an overdose of adefovir. No SAE were associated with the events. No AEs were associated with these overdoses. Also, there were no notable changes in serum creatinine in two of the subjects. One subject had a serum creatinine concentration of 0.6 mg/dL from screening through Week 12, followed by an increase to 1.0 mg/dL at Week 24, a decrease to 0.6 mg/dL at Week 36 when the dosing error was identified, 0.7 mg/dL at Weeks 44 and 48, and 0.8 at Week 84.
- Expired medication: one subject received an expired medication for two weeks. Liver enzyme (ALT) did not change during this period.
- Prohibited concomitant medication use: none reported

Demographics

The demographic and disease characteristics of patients enrolled in the study are listed in Tables 4, 5 and 6.

Slightly more than one third of the subjects were female. The majority of the subjects (60% of the active group and 70% of placebo group) were Caucasian, followed by Asian (~20% in each group), and Black (10% in active group and 5% in placebo group). The larges cohort of the subjects (83/173, 48%) were 12 to <18 years of age (56 in active group and 27 in the placebo group).

Table 4: Demographic characteristics

	2−6 Years a		7−11 Years a		12−17 Years a		Total	
Baseline Characteristics	**ADV (n=23)**	**PLB (n=12)**	**ADV (n=36)**	**PLB (n=19)**	**ADV (n=56)**	**PLB (n=27)**	**ADV (n=115)**	**PLB (n=58)**
Sex (n, %)								
Female	14 (61%)	8 (67%)	13 (36%)	4 (21%)	14 (25%)	7 (26%)	41 (36%)	19 (33%)
Male	9 (39%)	4 (33%)	23 (64%)	15 (79%)	42 (75%)	20 (74%)	74 (64%)	39 (67%)
Age (years)								
Median	4.0	5.0	10.0	10.0	14.0	14.0	11.0	11.0
Min, Max	2.0, 6.0	2.0, 6.0	7.0, 11.0	8.0, 11.0	12.0, 17.0	12.0, 17.0	2.0, 17.0	2.0, 17.0
Race (n, %)								
White	6 (26%)	3 (25%)	23 (64%)	17 (90%)	41 (73%)	21 (78%)	70 (61%)	41 (71%)
Asian	8 (35%)	6 (50%)	8 (22%)	1 (5%)	13 (23%)	5 (19%)	29 (25%)	12 (21%)
Black	7 (30%)	1 (8%)	3 (8%)	1 (5%)	1 (2%)	1 (4%)	11 (10%)	3 (5%)
American Indian or Alaska Native	0	0	0	0	1 (2%)	0	1 (< 1%)	0
Other	2 (9%)	2 (17%)	2 (6%)	0	0	0	4 (4%)	2 (3%)
Ethnicity (n, %)								
Hispanic/Latino	0	0	0	0	1 (2%)	0	1 (< 1%)	0
Weight (kg)								
Male Mean (SD)	17.5 (2.63)	18.0 (3.42)	33.3 (9.44)	36.0 (8.86)	61.6 (16.07)	63.4 (16.67)	47.5 (21.48)	48.2 (21.09)
Female Mean (SD)	16.8 (3.76)	19.0 (4.48)	31.3 (8.12)	30.1 (8.23)	52.7 (13.31)	47.5 (16.29)	33.7 (17.58)	31.9 (16.64)

As mentioned in the Protocol Deviation section, there were 34/173 (20%) subject with either one or both of the screening/confirmatory screening visits serum ALT values below 1.5 x ULN. Seventeen subjects had one of the values <1.5 x ULN; another 17 subjects had both values < 1.5 x ULN. Out of these 34 subjects, 19 (56%) had baseline ALT value that was also <1.5 x ULN. Thirty seven (16%) of the total 173 subjects had baseline ALT < 1.5 x ULN. Of those, 20 (74%) subjects had baseline ALT <1.2 x ULN. One hundred and one subjects (101/173, 58%) had

baseline ALT >2x ULN. The mean baseline ALT value by age and treatment group and mean ULN for these baseline values are displayed in Table 5. At baseline, 3 subjects were found to have negative HBeAg (all with + HBeAb). All three subjects did have documented positive HBeAg at screening.

Table 5: Baseline Disease Characteristics (Applicant's Analyses)

	2−6 Years a		7−11 Years a		12−17 Years a		Total	
	ADV (n=23)	**PLB (n=12)**	**ADV (n=36)**	**PLB (n=19)**	**ADV (n=56)**	**PLB (n=27)**	**ADV (n=115)**	**PLB (n=58)**
HBV DNA (log10 copies/mL)								
Mean (SD)	9.23 (0.6)	9.01 (1.2)	8.63 (0.7)	8.52 (0.6)	8.60 (1.0)	8.63 (1.0)	8.74 (0.9)	8.67 (1.0)
Min, Max	8.27, 10.3	5.44, 10.25	6.72, 10.2	7.22, 9.40	5.20, 9.91	5.40, 10.26	5.20, 10.30	5.40, 10.26
HBeAg (n, %)								
Negative	0	1 (8%)	0	0	2 (4%)	0	2 (2%)	1 (2%)
Positive	23 (100%)	11 (92%)	36 (100%)	19 (100%)	54 (96%)	27 (100%)	113 (98%)	57 (98%)
HBsAg b (n, %)								
Negative	0	0	0	0	0	0	0	0
Positive	23 (100%)	12 (100%)	36 (100%)	19 (100%)	56 (100%)	27 (100%)	115 (100%)	58 (100%)
ALT (U/L)								
Mean (SD)	90 (54)	105 (65)	105 (61)	81 (25)	123 (100)	109 (59)	111 (82)	99 (53)
Min, Max	33, 227	49, 265	23, 249	43, 130	24, 448	31, 250	23, 448	31, 265
(x ULN)								
Mean (SD)	2.6 (1.6)	3.1 (1.9)	2.8 (1.7)	2.1 (0.8)	3.0 (2.4)	2.7 (1.4)	2.9 (2.0)	2.6 (1.4)
Min, Max	1.0, 6.7	1.4, 7.8	0.7, 6.0	1.1, 3.8	0.7, 10.4	0.7, 5.8	0.7, 10.4	0.7, 7.8

A slight majority of the subjects had history of previous treatment for CHB infection (Table 6). The 8 subjects listed as having previous treatment history with adefovir participated in the Phase 1/2 pediatric study (GS-02-517) prior to enrolling in this phase 3 study.

Table 6: Prior Treatment for CHB

	All ADV N= 115	**All Placebo N= 58**	**Overall N= 173**
Any prior Medication	66(57)	33(57)	99(57)
Lamivudine	46(40)	23(40)	69(40)
IFN	52(45)	28(48)	80(46)
ADV	4(4)	4(7)	8(5)
other	8(7)	2(3)	10(6)

Efficacy Findings

Forty-eight percent of subjects (83/173) received tablet (56 active, 27 placebo); fifty-two percent (90/173) received the oral suspension (59 active, 31 placebo). Exposure and disposition is summarized in Table 7.

Table 7: Exposure and disposition

	tablet N= 83	**suspension N= 90**
	n(%)	n(%)
Exposure for ≥ 48 weeks	80 (97)	90 (100)
Discontinued ≤Week 48	3 (3)	0

Overall, 98% (170/173) of patients completed 48 weeks of blinded therapy. Only 3 subjects discontinued prior to Week 48. All three subjects received adefovir tablet. One subject discontinued due to AE; 2 subjects were non-compliant (one was actively withdrawn, one was lost to follow-up). The study is designed to administer 48 weeks of blinded therapy followed by open-label treatment with adefovir which was originally designed to last for up to 240 weeks. The open-label period lasted until week 144.

Primary Efficacy Endpoint
The primary efficacy endpoint was defined as the proportion of subjects with HBV DNA <1000 copies/mL plus normalization of ALT by the end of the blinded treatment period (Week 48).
The Applicant's analyses (Table 8) showed that overall, the proportion of subjects with HBV DNA <1000 copies/mL plus normal ALT value by Week 48 was significantly more in those who received active treatment (adefovir) than those who received placebo (19% vs. 2%, $p<0.001$). The Sponsor further analyzed the outcome based on age and treatment type received. As shown in Table 8, the oldest age group (12-<18 years) was the only group for which the proportion of adefovir treated subjects was statistically different compared to placebo (23% vs. 0%, $p = 0.007$). This is also the group that received tablet formulation.

This result should be interpreted with caution. First, the study was not designed (powered) to allow assessment difference in treatment response based by age group. Second, the likelihood of response to treatment depends on whether the patient is immunotolerant – defined normal or near normal serum ALT, very high serum HBV DNA level and persistent HBsAg and HBeAg positivity.

Also, as there was no overlap in adefovir formulation used between the younger and older age group (2-<12 and 12->18), it was prudent to demonstrate that the apparent lack of effectiveness of the drug was not due to chemistry or pharmacology deficiencies. The data for chemistry and clinical pharmacology have been reviewed by the respective disciplines and no deficiencies were found, that is, the suspension formulation was a stable, acceptable formulation and provided the targeted adefovir exposure in all age groups.

Table 8: Proportion of subjects with HBV DNA <1000 plus normalization of ALT by age Applicant's analyses

HBV DNA <1000 copies/mL and Normal ALT (n, %)	2−6 Years a		7−11 Years a		12−17 Years		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Baseline	0	0	0	0	0	0	0	0
Week 24	0	0	2 (6%)	0	4 (7%)	0	6 (5%)	0
End of Blinded Treatment	3 (13%)	1 (8%)	6 (17%)	0	13 (23%)	0	22 (19%)	1 (2%)
p-value	p = 1.00		p = 0.083		p = 0.007		p < 0.001	

The discrepancy between the Sponsor and this reviewer (Table 9) for this analysis is in treatment group 1- where there is one less subject identified as responder by the Sponsor. This subject had an ALT of 34 U/L and HBV DNA of 168 copies/mL at the Week 48 visit. The upper limit of normal was defined as 34 U/L. While this reviewer considered ≤ 1x ULN as normalization, the Applicant may have considered < 1 x ULN as normalization. Because these subgroups- particularly in the age 2-<12 years old- have small number of subjects enrolled, even one subject may skew the efficacy endpoint results. As seen in Table 9, the efficacy result for group 1 increases from 13% (as per the Applicant), to 17%. Although the proportion has increased numerically, the difference in treatment effect remains statistically insignificant (p=0.634) when compared to placebo. Analyses of the primary efficacy endpoint by Dr. Karen Qi, Biometrics Statistical Reviewer was similar to this reviewer's result. Please refer to Dr. Qi's review for additional details.

Table 9: Proportion of subjects with HBV DNA <1000 plus normalization of ALT by age Reviewer's Analyses

HBV DNA <1000 copies/mL and Normal ALT (n, %)	2−6 Years a		7−11 Years a		12−17 Years		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Baseline	0	0	0	0	0	0	0	0
End of Blinded Treatment	4 (17%)	1 (8%)	6 (17%)	0	13 (23%)	0	23 (20%)	1 (2%)
p-value	p =.634		p =.083		p =.007		p <.001	

When the tablet formulation is compared to the suspension formulation (Table 10), the number of responders using suspension is 10/57 (18%) for the adefovir group and 1/31(3%) for the placebo group. The data as presented in Table 10 does suggest that for a reason not determined (other than the possibilities discussed below), only the older subjects (12-<18), who also happen to have received the tablet formulation, did have a statistically significant response compared to placebo. By combining the two younger age groups, the number of subjects who received the suspension formulation was increased to 90, which is slightly more than the older age group (n= 83). Despite the consolidation to increase the number of subjects in the analysis, the difference in

treatment response (when compared to placebo) seen with suspension formulation remains not statistically significant (p=0.089). Again, the study was not designed to evaluate efficacy by formulation or age and as discussed, this outcome was not a result of poor quality of the suspension formulation- as it was deemed sufficient by the Agency. The result may also be confounded by other variables which were not controlled. Variables such as baseline ALT, baseline HBV DNA, HBeAg, race, previous history of treatment for HBV, and genotype were evaluated to see their effect on treatment response.

Table 10: Proportion of subjects with HBV DNA <1000 plus normalization of ALT by Formulation Reviewer's Analyses

HBV DNA <1000 copies/mL and Normal ALT (n, %)	Suspension Formulation 2- <12 Years		tablet Formulation 12- <18 Years	
	ADV (n=59)	PLB (n=31)	ADV (n=56)	PLB (n=27)
Baseline	0	0	0	0
End of Blinded Treatment	10 (17%)	1 (3%)	12 (23%)	0
p-value	p =0.089		p =0.007	

Secondary Efficacy Endpoints

Multiple secondary efficacy endpoints have been evaluated by the Applicant, this reviewer and Dr. Qi. Based on literature review, among the most important variable considered to have significant effect on treatment response is baseline ALT value. As discussed previously, it is an important disease characteristic that has been identified as likely to increase response to treatment. Additional efficacy endpoints used for subanalyses include: analyses by HBeAg loss or seroconversion, by baseline HBV DNA, by history of previous treatment, by race, and by HBV DNA genotype.

Analyses by Baseline ALT

Assessment of baseline ALT has become a critical step for most pediatric hepatologists when contemplating initiation of therapy for CHB infection. Although the protocol was amended to enroll patients with screening ALT value >1.5 ULN (at both screening and confirmatory screening visits- i.e. events -10 and -9), as many as 34/173 (20%) subjects had ALT values < 1.5 ULN at one or both visits. Of these 34 subjects, 19 (56%) also had a baseline ALT value that was also <1.5 x ULN. Thirty seven (16%) of the total 173 subjects had baseline ALT < 1.5 x ULN. Seventy one subjects had a baseline ALT value less than or equal to 2 x ULN. Therefore, the total number of subjects used for such analyses becomes smaller. This in turn affects the ability to derive statistically significant results demonstrating that subjects with elevated baseline ALT have a higher response rate to treatment with adefovir when compared to placebo.

Table 11 shows the proportion of subjects with baseline ALT > 1.5 x with HBV DNA <1000 and normal ALT by end of blinded treatment period. Nineteen percent of the adefovir group versus two percent of the placebo group was responsive. This analyses shows that overall, the adefovir treated group had a response that was statistically significant compared to placebo. The difference in response when compared to placebo was not statistically significant in cohorts 1

and 2. Again it is difficult to draw any firm conclusions from these results as the number of subjects per cohort is small.

Table 11: Subjects with HBV DNA <1000 c/mL and normal ALT by baseline ALT Reviewer's Analyses

	2−<7 Years (suspension)		7− <12 Years (suspension)		2-<12 Years (suspension)		12−17 Years (tablet)		Total	
	ADV (n=23) G 1	PLB (n=12) G2	ADV (n=36) G3	PLB (n=19) G4	ADV (n= 59)	PLB (N= 31)	ADV (n=56) G5	PLB (n=27) G6	ADV (n=115)	PLB (n=58)
Baseline ALT >**1.5** ULN	17/23 (74)	11/12 (92)	28/36 (78)	14/19 (74)	45/59 (76)	25/31 (81)	40/56 (71)	19/27 (44)	85/115 (74)	44/58 (76)
HBV DNA <1000 copies/mL and Normal ALT by Week 48	3 (18%)	1 (9%)	5 (18%)	0	8 (18%)	1 (4%)	8 (20%)	0	16 (19%)	1 (2%)
p-value	p =1.000		p =0.151		p =0.143		p 0.045		p =0.01	

Tables 12 - 13 summarize treatment response when using baseline ALT ≥ 2 x ULN. Here too, the overall response was statistically significant for adefovir compared to placebo (21% vs. 0%, p= 0.002) and supports the primary efficacy endpoint outcome. However, the difference in response when compared to placebo was not statistically significant across all cohorts. Of note, the number of subjects available for this sub-group analysis was even smaller.

Table 12: Subjects with HBV DNA <1000 c/mL and normal ALT by baseline ALT Reviewer's Analyses

	2−<7 Years (suspension)		7− <12 Years (suspension)		2-<12 Years (suspension)		12−17 Years (tablet)		Total	
	ADV (n=23) G 1	PLB (n=12) G2	ADV (n=36) G3	PLB (n=19) G4	ADV (n= 59)	PLB (N= 31)	ADV (n=56) G5	PLB (n=27) G6	ADV (n=115)	PLB (n=58)
Baseline ALT **≥2** ULN	13/23 (74)	7/12 (92)	22/36 (78)	10/19 (74)	35/59	17/31	35/56 (71)	15/27 (44)	70/115 (74)	32/58 (76)
HBV DNA <1000 c/mL and Normal ALT by Week 48	3 (23%)	0	5 (23%)	0	8 (23%)	0	7 (20%)	0	15 (21%)	0
p-value	p =0.521		p =0.155		p=0.42		p =0.087		p =0.002	

Table 13: Subjects with HBV DNA <1000 c/mL and normal ALT by baseline ALT (>2xULN) Statistician's Analyses

	2-6 years		7-11 years		12-17 years		total	
	Adefovir (n=23)	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
n (%)	3/13 (23%)	0/7 (0%)	5/22 (23%)	0/9 (0%)	7/35 (20%)	0/15 (0%)	15/70 (21%)	0/31 (0%)
p-value based on Fisher's exact test	0.521		0.286		0.087		0.005	

Analyses by HBeAg Loss or Seroconversion

All subjects were positive for HBeAg at screening. However, three subjects had negative HBeAg and positive HBeAb by the time they presented at baseline visits. Two of these subjects were in the adefovir group (group 5) and one subject was in the placebo group (group 2). All three subjects were excluded from analyses by HBeAg loss or seroconversion by the end of the blinded treatment period. Table 14 summarizes results of HBeAg loss, without consideration to HBV DNA level or ALT value at the end of the blinded treatment period. The overall proportion of subjects with HBeAg loss is numerically higher in the adefovir arm compared to placebo, although not statistically significant. A statistically significant difference in HBeAg loss was not seen in any age group. Similarly, HBeAg seroconversion was noted to be more in the adefovir group 16% vs. 5-7% in the placebo group (Table 15). Here too, there was no statistically significant difference observed between placebo and adefovir in any age group. This apparent decreased response (as assessed by HBeAg loss) in the older age group was also noted with lamivudine (see discussion below).

Table 14: Proportion of Subjects with HBeAg loss at End of Blinded Treatment period Applicant's Analyses*

HBeAg loss (n, %)	**2−6 Years**		**7−11 Years**		**12−17 Years**		**Total**	
	ADV (n=23)	**PLB (n=11)**	**ADV (n=36)**	**PLB (n=19)**	**ADV (n=54)**	**PLB (n=27)**	**ADV (n=113)**	**PLB (n=57)**
Baseline	0	0	0	0	0	0	0	0
End of Blinded treatment	5(22%)	0	7(19%)	0	7(13%)	3(11%)	19(17%)	3(5%)
p-value	P=0.15		P=0.082		P=1.00		P=0.051	

*This reviewer's analyses of the proportion of subjects with HBeAg loss at the end of blinded treatment period was similar to that of the Applicant's analyses except the reviewer has one additional subject in cohort 3 (placebo group) as being responsive (i.e. 4/27 = 15%).

Table 15: Proportion of Subjects with HBeAg Seroconversion at End of Blinded Treatment period Applicant's Analyses*

HBeAg seroconversion, (n, %)	2−6 Years		7−11 Years		12−17 Years		Total	
	ADV (n=23)	PLB (n=11)	ADV (n=36)	PLB (n=19)	ADV (n=54)	PLB (n=27)	ADV (n=113)	PLB (n=57)
Baseline	0	0	0	0	0	0	0	0
End of Blinded treatment	5(22%)	0	7(19%)	0	6(11%)	3(11%)	18(16%)	3(5%)
P value	p = 0.15		p = 0.082		p = 1.00		p = 0.051	

*This reviewer's analyses of the proportion of subjects with HBeAg loss at the end of blinded treatment period was similar to that of the Applicant's analyses except the reviewer has one additional subject in cohort 3 (placebo group) as being responsive (i.e. 4/27 = 15%).

The overall proportion of subjects with HBeAg seroconversion, HBV DNA <1000 c/mL, and normalization of ALT value at end of blinded treatment period was higher in the adefovir arm compared to placebo (12% vs. 0) (Table 16-18).

Table 16: Proportion of Subjects with HBeAg seroconversion, HBV DNA <1000 c/mL, Normal ALT at End of Blinded Treatment Period Reviewer's Analyses

HBeAg seroconversion HBV DNA <1000 c/mL, Normal ALT (n, %)	2−6 Years		7−11 Years		12−17 Years		Total	
	ADV (n=23)	PLB (n=11)	ADV (n=36)	PLB (n=19)	ADV (n=54)	PLB (n=27)	ADV (n=113)	PLB (n=57)
Baseline	0	0	0	0	0	0	0	0
End of Blinded treatment	4(17%)	0	5(14%)	0	4(7%)	0	13(12%)	0

Further analyses was performed using proportion of subjects with HBeAg seroconversion, HBV DNA <1000 c/mL, and normalization of ALT value by baseline ALT value (Tables 21-22). The result remains consistent in that overall, the adefovir arm had 16% response vs. 0% with placebo treatment.

Table 17: Proportion of Subjects with HBeAg seroconversion, HBV DNA <1000 c/mL, Normal ALT at End of Blinded Treatment period by Baseline ALT Reviewer's Analyses

	2−6 Years		7−11 Years		12−17 Years		Total	
	ADV (n=23)	PLB (n=11)	ADV (n=36)	PLB (n=19)	ADV (n=54)	PLB (n=27)	ADV (n=115)	PLB (n=57)
Baseline ALT >2 ULN	13	7	22	10	35	15	70	32
Baseline HBeAg seroconversion	0	0	0	0	0	0	0	0
HBeAg seroconversion by week 48	4/13(13%)	0	7/22(32%)	0	6/35(17%)	4/15(27%)	17/70(24%)	4/32(13%)
Baseline ALT >2ULN, HBeAg conversion, HBV DNA <1000, Normal ALT at Week 48	3/13(23)	0	5(23)	0	3(9)	0	11(16)	0

Analyses By baseline HBV DNA

The mean HBV DNA log was 8.8 copies/mL. No subject in the placebo group (regardless of baseline HBV DNA level), with baseline ALT >2xULN had an HBV DNA decrease to <1000 copies/mL and normalization of ALT by Week 48. For the adefovir arm, subjects with less than the mean HBV DNA copies/mL had a better response to treatment (36%) than those with HBV DNA levels higher than the mean (15%). Table 18 summarizes this finding.

Table 18: Proportion of Subjects with HBV DNA <1000 plus Normalization of ALT by Baseline HBV DNA and ALT Reviewer's Analyses

	2−6 Years a		7−11 Years a		12−17 Years	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)
Baseline HBV DNA log <8.8 and ALT >2xULN w/ HBV DNA <1000 copies/mL and Normal ALT @ 48 wks	2/4 (50)	(0)	5/14 (36)	(0)	5/14 (36)	(0)
Baseline HBV DNA log >8.8 and ALT >2xULN w/ HBV DNA <1000 copies/mL and Normal ALT @ 48 wks	(0)	(0)	(0)	(0)	3/21 (15)	(0)

Analyses by Race

Regardless of race, all subjects in the adefovir group had better treatment response compared to the placebo group. The number of Black subjects (n= 14) was much less than the total number of Asians (n= 41) or Caucasians (n= 111). It is therefore not surprising that treatment response was least significant in the Black subjects. These findings are summarized in Tables 19 and 20.

Table 19: Proportion of subjects with HBV DNA <1000 plus normalization of ALT by Race and Age

	2−6 Years		7−11 Years		12−17 Years		Total	
	ADV (n=23)	**PLB (n=12)**	**ADV (n=36)**	**PLB (n=19)**	**ADV (n=56)**	**PLB (n=27)**	**ADV (n=115)**	**PLB (n=58)**
Asian	N=8	6	8	1	13	5	29	12
	1/8 (13)	0	1/8 (13)	0	3/13(23)	0	5 (17)	0
Black	N=7	1	3	1	1	1	11	3
	1/7 (14)	0	0	0	0	0	1 (9)	0
Caucasian	N=6	3	23	17	41	21	70	41
	2/6 (33)	1/3 (33)	4/23 (17)	0	10/41(24)	0	16(23)	1(2)

Table 20: Proportion of subjects with HBV DNA <1000 plus normalization of ALT by Baseline ALT (>2ULN) Race and Age

	2−6 Years		7−11 Years		12−17 Years		Total	
	ADV (n=23)	**PLB (n=12)**	**ADV (n=36)**	**PLB (n=19)**	**ADV (n=56)**	**PLB (n=27)**	**ADV (n=115)**	**PLB (n=58)**
Asian	N=3	3	6	0	11	2	20	5
	1/3 (33)	0	1/6(17)	0	2/11(18)	0	4 (20)	0
Black	N=5	1	2	1	1	1	8	3
	0	0	0	0	0	0	0	0
Caucasian	N=4	1	12	9	23	12	39	22
	2/4 (50)	0	3/12 (25)	0	5/23(22)	0	10(26)	0

Analyses by HBV DNA Genotype

A majority of subjects had genotype A. Not surprisingly, subjects with genotypes A and C had the most response to treatment (Table 21).

Table 21: Proportion of subjects with HBV DNA <1000 plus normalization of ALT by viral genotype and Age Reviewer's Analyses

	2-6 years		7-11 years		12-17 years		total	
HBV Genotype	**Adefovir (n=23)**	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
A	3/5 (60%)	0/1 (0%)	2/17 (12%)	0/13 (0%)	9/29 (31%)	0/18 (0%)	14/51 (27%)	0/32 (0%)
B	0/4 (0%)	0/3 (0%)	1/3 (33%)	0/1 (0%)	1/6 (17%)	0/1 (0%)	2/13 (15%)	0/5 (0%)
C	1/1 (100%)	0/1 (0%)	1/4 (25%)	0/0	1/5 (20%)	0/3 (0%)	3/10 (30%)	0/4 (0%)
D	0/11 (0%)	1/5 (20%)	2/9 (22%)	0/4 (0%)	2/15 (13%)	0/5 (0%)	4/35 (11%)	1/14 (7%)
E	0/2 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/0	0/0	0/3 (0%)	0/2 (0%)
F	0/0	0/0	0/1 (0%)	0/0	0/1 (0%)	0/0	0/2 (0%)	0/0

Comparison to Adult Treatment with Adefovir

The two pivotal adult studies of adefovir enrolled HBeAg positive (study 437, N= 329) and HBeAg negative patients (Study 438, N =178). The primary efficacy endpoint in both studies was histological improvement at week 48. Therefore, direct comparison of the primary efficacy endpoint cannot be made to the primary efficacy endpoint used in this pediatric study. If comparing the overall response to treatment (i.e. the proportion of subjects who met the primary efficacy endpoint) 53-64% of the adult subjects had improvement following active treatment compared to 25-35% of the placebo treated subjects. Similarly, in the pediatric study (Study 518), the proportion of subjects who responded to adefovir is more when compared to placebo (20% vs. 2%).

Comparison to Antiviral Drugs Previously Approved for CHB in Children

Lamuvidine was approved for use in children in 2001. The pivotal phase 3 study was a double-blind, placebo controlled, multi-center trial of safety and efficacy of lamivudine in pediatric patients with CHB. Eligible subjects were aged 2-17 years with CHB, liver biopsy evidence of inflammation and with baseline ALT values of 1.3 x ULN. Two hundred eighty-eight subjects were randomized to received 52 weeks of lamivudine 3mg/kg daily (maximum of 100mg/day) or placebo in a 2:1 ratio. The primary efficacy endpoint was the proportion of subjects with a complete virologic response (CVR) at week 52- defined as loss of HBeAg and undetectable HBV DNA levels. The methodology used to detect HBV DNA was less sensitive and different than what is used for the adefovir study. Complete virologic response was seen in 23% (44/191) of lamivudine subjects and 13% (12/95) of placebo subjects (p=0.037).The statistically significant difference was maintained after analyses of several different treatment populations. In

addition, a greater proportion of subjects with higher ALT values and lower HBV DNA levels had a complete virologic response. The proportion of subjects with baseline ALT < 2x ULN with CVR was 12% for lamivudine and 8% for placebo. The response for those with baseline ALT >5x ULN was 50% for the lamivudine group and 24% for the placebo group. Treatment response was noted to be higher in the younger age groups: 33% lamivudine vs. 8% placebo in the 2-6 years old group; 21% lamivudine vs. 16% placebo in the 7-12 age group; and 17% lamivudine vs. 15% placebo in the 13-17 years age group. However, this difference in age response was confounded by baseline ALT level, HBV DNA levels and histology. The effect of age on HBV DNA response and ALT normalization was examined and no statistically significant difference was noted with either of the endpoints. HBeAg loss was uncommon, seen in 26% lamivudine and 15% placebo treated subjects. HBeAg seroconversion was reported in 25% lamivudine and 15% placebo subjects.

It is inappropriate to directly compare results from the lamivudine trial to the adefovir trial. If loosely compared, there are some similarities such as the age group studied, the study design-double blind and placebo controlled with 2:1 ratio. The number of subjects enrolled is somewhat higher in the lamivudine study. The primary efficacy endpoints used for the two studies are different. The primary efficacy endpoint for lamivudine was the proportion of subjects with loss of HBeAg and undetectable HBV DNA levels. HBeAg loss was evaluated as a secondary endpoint for adefovir study.

When comparing the primary efficacy endpoint results for the two studies, both active drugs have statistically significant response compared to placebo. Furthermore, effect of baseline ALT on treatment outcome was shown with both drugs. For lamivudine, the response (loss of HBeAg and undetectable HBV DNA levels) for those with baseline ALT >5x ULN was 50% for the lamivudine group and 24% for the placebo group. Similarly, response (HBeAg loss, HBV DNA <1000, Normalization of ALT) for those with baseline ALT ≥ 2x ULN was 16% for the adefovir group and 0% for the placebo group.

In comparing HBeAg loss results between the two studies, there are general similarities; the proportion of subjects with treatment response was higher in subjects who received active treatment in both studies. HBeAg seroconversion was reported in 25% lamivudine and 15% placebo subjects; response (seroconversion) was 16% in subjects treated with adefovir and 5% in the placebo group.

It is interesting that when comparing the primary efficacy endpoints between the two studies, lamivudine appeared to be more effective in younger patients while adefovir appeared to be less effective in younger patients. However, when comparing by the actual efficacy variable (i.e. HBeAg loss or seroconversion) it hold true that in both studies, the younger age groups appeared to have responded more to adefovir than to placebo.

Clinical Microbiology

Please see Dr. Lalji Mishra's review for full review of Clinical Microbiology. Briefly, on-therapy isolates from placebo arm subjects did not develop any new conserved site substitutions

in HBV Pol at week 48 compared to baseline isolates. On-therapy isolates from 5 experienced and 2 naïve subjects in the adefovir arm developed new conserved sites substitutions in HBV Pol at week 48 compared to baseline isolates. None of the on-therapy isolates developed rtA181IV and rtN236T associated with adefovir resistance in adult studies.

Efficacy Conclusions

The efficacy data support the conclusion that pediatric patients between 12 - < 18 years of age who were treated with Hepsera® tablet demonstrated a treatment difference that was statistically significant when compared to placebo. Comparison of response by age yielded differences among the 3 cohorts, with only the oldest age group having demonstrated a treatment difference that was statistically significant when compared to placebo. Despite performing multiple subanalyses, the younger age groups (2-<12 years) failed to demonstrate a statistically significant difference in treatment response when compared to placebo groups. The reason for the apparent age difference in response to therapy remains undetermined but there are few reasonable explanations. First, there may well be a relationship between the small number of subjects studied and treatment outcome, as the study was not designed or powered to analyze effect of age on treatment response. Therefore, the conclusions should be interpreted with caution. In addition, adefovir does not appear to be a very potent hepatitis B drug. To show its modest effect, the number of subjects treated may well need to be much higher. Furthermore, children in the younger age group are known to be in an immunotolerant phase, decreasing their likelihood of response to treatment. The apparent decreased response seen in the younger age group is thus biologically plausible

Finally, there were no new microbiology issues identified that require changes in the labeling for Hepsera® tablet or how it is used in clinical practice.

The magnitude of effect of adefovir was not large. However, it did demonstrate robustness as the p-value remained low even with multiple subgroup analysis such as baseline ALT. These results provide evidence that adefovir may be of benefit to subset of pediatric patients who may lack other treatment options such as those with previous history of treatment for CHB.

7. REVIEW OF SAFETY

Methods and Findings

Safety data from the blinded treatment period were reviewed. Safety data were reported for all subjects who received at least one dose of the study drug. Clinical adverse events were then described by organ system involved and type of adverse event. Extent of exposure, discontinuation and interruptions, common adverse events, adverse events related to study drug, severe adverse events, serious adverse events, deaths, adverse events of special interests, laboratory adverse, vital signs and growth were reviewed and discussed below.

Eliciting adverse events data in the development program

Safety was evaluated by collection of adverse events (AEs), HBV-related events, clinical laboratory testing (including hematology and chemistry), physical examination, vital signs measurements, and growth. Vital signs, physical examinations, concomitant medications, AE assessments and clinical laboratory evaluations were performed at Screening, Baseline, and every 4 weeks to week 12, and then every 12 weeks from weeks 12 to 48. Additional assessments of hepatitis status were performed at specified study visits.

Appropriateness of adverse event categorization and preferred terms

All adverse events reported in studies in which patients received at least one dose of adefovir were reviewed. In general, the review focused on known adefovir associated adverse events that occurred in adults and reviewed in the adult NDA. The Sponsor coded AEs according to MedDRA and the coding was reasonable.

Extent of Exposure

With the exception of 3 subjects, all subjects completed 48 weeks of treatment. The three subjects who discontinued were all in the adefovir arm (group 6- age 12-<18 years).

Table 22: Extent of Exposure Applicant's Analyses

	2−6 Years a		7−11 Years a		12−17 Years a		Total	
	ADV (n=23)	**PLB (n=12)**	**ADV (n=36)**	**PLB (n=19)**	**ADV (n=56)**	**PLB (n=27)**	**ADV (n=115)**	**PLB (n=58)**
Subjects Completing	23	12	36	19	53	27	112	58
Blinded Treatment (n, %)	(100%)	(100%)	(100%)	(100%)	(95%)	(100%)	(97%)	(100%)
Extent of Exposure (weeks):								
Mean (SD)	47.6 (1.22)	48.0 (0.34)	47.9 (0.30)	47.6 (0.72)	46.1 (8.19)	48.0 (0.30)	47.0 (5.78)	47.9 (0.50)
Median	48.0	48.1	47.9	48.0	48.0	48.0	48.0	48.0
Q1, Q3	47.9, 48.1	48.0, 48.1	47.9, 48.1	47.4, 48.1	47.9, 48.1	47.9, 48.1	47.9, 48.1	47.9, 48.1
Min, Max	42.7, 48.9	47.0, 48.3	47.3, 48.7	45.9, 48.3	4.3, 49.0	47.3, 48.7	4.3, 49.0	45.9, 48.7

Adverse Events Leading to Treatment Discontinuation or Interruption

One subject permanently discontinued treatment with adefovir due to an adverse event. This was an adolescent male (12-17 years) with previous history of psychological (behavioral) disorder. The event was reported as a SAE judged to be unrelated to study treatment. The subject started study treatment on 01 October 2004. He exhibited Grade-2 abnormal behavior ("worsening of a

behavioral disorder") from , which led to discontinuation of treatment. He was hospitalized for 2 days because of Grade-2 "drug intoxication" after taking Rivotril® (clona l® (clomipramine HCl), Effortil® (etilefrine HCl), and alprazolam, reportedly due to school problems. He was readmitted to the hospital on because of violent behavior, and he remained in the psychiatric unit until . Cannabis was detected in a urine sample obtained on .

Two adefovir treated subjects (2%) and two placebo-treated subjects (3%) had dose interruptions because of AEs. All of these events were judged unrelated to study treatment. Events leading to interruption of adefovir treatment were Grade-2 "drug intoxication" as discussed above; and Grade-1 pyrexia, viral gastroenteritis, and a skin laceration in one subject, where each event resulted in a separate 1-day treatment interruption. No subject had a dose reduction because of an AE.

Table 23 summarizes AEs leading to treatment discontinuation and interruption and overall treatment emergent and treatment related AEs. Treatment emergent AEs were similar between adefovir and placebo group. Treatment related AEs were slightly more in adefovir treated subjects. Treatment related SAEs were reported more frequently in the placebo arm as were Grade 3 and 4 AEs, placebo group (10%) compared to the adefovir group (2%). Please refer to the Serious and Severe Adverse Events sections for details.

Table 23: Adverse Events

	ADV N= 115(%)	PLB N= 58(%)	Total N= 173(%)
AE leading to discontinuation	1 (1)	0	1 (<1)
AE leading to treatment interruption	2 (2)	2 (3)	4 (2)
Treatment emergent AE	95 (83)	48 (83)	143 (83)
Treatment related AE	16 (14)	6 (10)	22 (13)
SAE	7 (6)	5 (9)	12 (7)
Treatment Related SAE	1 (1)	2 (3)	3 (2)
Grade 3 and 4 AE	2 (2)	6 (10)	8 (5)

Common Adverse Events

The adverse event profile of adefovir was well characterized during the larger adult studies. The most common treatment events in the pediatric study are listed below.

In both the adefovir and placebo groups, 83% of subjects reported at least one treatment-emergent AE. Most events were Grade 1 or 2 and judged by the investigator to be unrelated to study treatment. The most common events were typical childhood illnesses such as abdominal pain, cough, headache, nasopharyngitis, pharyngitis, pyrexia, and upper respiratory tract infection. Rate of occurrence in the adefovir group was not significantly different from the rate in the placebo group. Three subjects (3%) in the adefovir group had urticaria. Urticaria was not reported as treatment-related AE occurring in ≥ 3% of subjects in the adult studies. **Treatment-**

emergent AEs that were reported in at least 1% of adefovir treated subjects or placebo-treated subjects are summarized in Table 24.

Table 24: Treatment Emergent Adverse Events

	ADV N=115	PLB N = 58
AEs		
Gastrointestinal Disorders	30 (26)	19 (33)
Nausea	4 (3)	1(2)
Vomiting	4 (3)	6 (10)
Diarrhea	8 (7)	4 (7)
Abdominal pain	15 (13)	12 (21)
Hepatobiliary Disorders	2(2)	2 (3)
Investigations	2(2)	1(2)
Increased ALT	2(2)	1(2)
Infection and Infestation	68 (59)	33 (57)
Respiratory Disorders	32 (28)	19 (33)
Nervous system Disorders		
Headache	18 (16)	8 (14)
Psychiatric Disorder	4 (3)	0
Skin and Soft Tissue Disorders	11(10)	9 (16)
Urticaria	3 (3)	0
Hypersensitivity reaction	0	1(2)
Allergic dermatitis	1(1)	
Musculo-skeletal Disorders	2 (2)	2(3)
Pain extremity	1(1)	0
Asthenia	2 (2)	
Metabolism and Nutrition Disorders		
Anorexia	5 (4)	0
Decreased Appetite	2 (2)	0

Adverse Events Related to Study Drug

Treatment-related AEs reported in ≥ 3% of all adefovir treated adult subjects include: asthenia (13%), headache (9%), abdominal pain (9%), nausea (5%), flatulence (4%), diarrhea (3%) and dyspepsia (3%).

Overall, 22 (13%) of the pediatric subjects experienced at least 1 AE considered related to study drug. Fourteen percent of the adefovir treated subjects and 10% of the placebo-treated subjects had at least one treatment-related AE during the blinded treatment period. Table 25 summarizes treatment-related AE by Organ Class System.

Table 25: Treatment-Related AE Applicant's Analyses

Treatment-Related AE by System Organ Class and Preferred Term (n, %)	2−6 Years b		7−11 Years b		12−17 Years b		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Subjects with ≥ 1 Treatment-Related AE	5 (22%)	2 (17%)	3 (8%)	2 (11%)	8 (14%)	2 (7%)	16 (14%)	6 (10%)
Blood and Lymphatic Disorders								
Thrombocytopenia	1 (4%)	0	0	0	0	0	1 (< 1%)	0
Gastrointestinal Disorders								
Abdominal Pain	0	0	1 (3%)	1 (5%)	1 (2%)	0	2 (2%)	1 (2%)
Diarrhea	0	0	2 (6%)	0	1 (2%)	0	3 (3%)	0
Nausea	1 (4%)	0	0	0	1 (2%)	0	2 (2%)	0
Vomiting	1 (4%)	0	0	0	0	0	1 (< 1%)	0
General Disorders								
Fatigue	0	1 (8%)	0	0	2 (4%)	1 (4%)	2 (2%)	2 (3%)
Hepatobiliary Disorders								
Hepatitis	0	1 (8%)	0	0	0	0	0	1 (2%)
Investigations								
ALT Increased	0	1 (8%)	0	0	1 (2%)	0	1 (< 1%)	1 (2%)
Hepatic Enzyme Increased	1 (4%)	0	0	0	0	0	1 (< 1%)	0
Blood CPK Increased	0	0	0	0	1 (2%)	0	1 (< 1%)	0
Metabolism and Nutrition Disorders								
Anorexia	1 (4%)	0	0	0	2 (4%)	0	3 (3%)	0
Decreased Appetite	0	0	0	0	1 (2%)	0	1 (< 1%)	0
Nervous System Disorders								
Headache	0	1 (8%)	1 (3%)	1 (5%)	0	0	1 (< 1%)	2 (3%)
Respiratory Disorders								
Epistaxis	0	0	0	1 (5%)	0	1 (4%)	0	2 (3%)
Skin and Subcutaneous Tissue Disorders								
Pruritus	0	0	1 (3%)	0	0	0	1 (< 1%)	0
Rash	1 (4%)	0	0	0	0	0	1 (< 1%)	0
Urticaria	1 (4%)	0	0	0	0	0	1 (< 1%)	0

In the adefovir group, one female subject (age 2-6 years old) had grade 3 SAE of increased hepatic enzymes. This treatment related AE resolved without treatment discontinuation or interruption. All other treatment-related events in adefovir treated subjects were Grade 1 or 2 and were judged to be non-serious and without leading to permanent discontinuation of study treatment. One adefovir treated subject (2-6 year old, male) had Grade-1 treatment-related thrombocytopenia that resolved by the next assessment without intervention; platelet count was recorded as 151 × 10^3/μL and increased to 352 × 10^3/μL by next visit- 30 days later). One adefovir treated subjects had urticaria.

Severe Adverse Events

Grade 3 and 4 adverse events at least possibly related to study medications reported in the clinical trials included hepatitis and increased hepatic enzyme (ALT).

Two subjects in the adefovir arm (2%) had Grade-3 AEs. One of the subjects experienced a Grade 3, SAE of increased hepatic enzymes (as discussed in the SAE section and the Hepatic AE section). The second subject had Grade-3 toothache and bronchitis. No subject had Grade 4 AE reported.

Six placebo-treated subjects (10%) had Grade-3 or 4 AEs. One subject had Grade-3 hepatitis ("severe hepatic flare"), an SAE which resolved without intervention; another subject had Grade-4 increased ALT, also an SAE which resolved without intervention.

Serious Adverse Events

Overall 12/173 (7%) patients experienced at least one serious adverse events. SAEs included: hepatitis, increased ALT, dyspepsia, gastritis, diarrhea, infection, fever, syncope and psychiatric disorder.

In the adefovir group, seven subjects (6%) had at least one SAE during the double-blind treatment period. One subject (2−6 years, female) had a treatment-related SAE (Grade-3 increased hepatic enzymes as discussed above in the treatment-related AE section; please see the Hepatic Events Section for further detail). No other subjects in the adefovir group developed hepatic related SAE. This was the only SAE related to hepatic status or function in the adefovir group. One male subject was hospitalized for gastritis. He had a history of abdominal pain. Endoscopy revealed chronic gastritis; an abdominal ultrasound was normal, and blood and urinalysis results were within normal limits. The subject received no treatment and study treatment was not interrupted; event was not considered related to adefovir. Pyrexia was the only SAE reported in more than one subject. One SAE in an adefovir treated subject resulted in permanent discontinuation of treatment due to "worsening of a behavioral disorder," (as discussed above in the treatment discontinuation section). There were no SAEs related to renal function in the adefovir group.

In the placebo group, 9% of subjects had at least one SAE. In two subjects (3%), the SAE was judged to be treatment related: Grade-4 increased ALT and Grade-3 hepatitis "severe hepatic flare". Table 26 summarizes all the SAEs reported for all treated subjects during the blinded treatment period.

Table 26: Serious Adverse Events

	2-6 years		7-11 years		12-18 years		Total	
	ADV N = 23	PLB N= 12	ADV N = 36	PLB N = 19	ADV N = 56	PLB N = 27	ADV N = 115	PLB N = 58
Subjects with ≥ SAE	3(13)	2(17)	1(3)	1(5)	3(5)	2(7)	7(6)	5(9)
SAEs								
Diarrhea	1(4)	0	0	0	0	0	1(<1)	0
Gastritis					1(2)		1(<1)	0
Dyspepsia						1(4)	0	1(2)
Hepatitis		1(8)						1(2)
Gastroenteritis				1(5)				1(2)
↑ALT		1(8)						1(2)
↑Hepatic Enzyme	1(4)						1(<1)	0
Pyrexia	1(4)		1(3)				2(2)	
Pneumonia						1(4)		1(2)
Syncope					1(2)		1(<1)	0
Abnormal Behavior					1(2)		1(<1)	0
Injury	1(4)				1(2)		2(2)	

Deaths

There were no deaths reported during the study period.

Adverse Events of Interest

Renal Adverse Events

Events in the "Renal and Urinary Disorders" system organ class were all judged unrelated to treatment. One adefovir treated subject (< 1%) and three placebo treated subjects (5%) had renal AEs. The adefovir treated subject, a male (12-17 age group) had a Grade-1 proteinuria from Day 132 to 137 that resolved without intervention. Treatment was continued and event was judged to be unrelated to treatment. The baseline creatinine for this subject was 0.1 mg/dL and at the end of blinded therapy, creatinine was 0.3 mg/dL. The creatinine clearance was recorded as 144 during baseline visit and was 160 at the end of blinded therapy. Events in placebo-treated subjects were enuresis, urinary frequency, and urinary incontinence.

Hepatic Adverse Events

The preferred terms for identifying AEs related to hepatic status or function in adefovir treated subjects were ALT increased, hepatic enzyme increased, and hepatomegaly. No adefovir treated subject showed evidence of hepatic decompensation. The preferred terms in the placebo treated subjects were hepatitis and ALT increased.

In the adefovir group, one event was a treatment-related SAE (Grade-3 hepatic enzyme increased), while the other hepatic AEs in this treatment group were judged to be non-serious. All hepatic AEs in adefovir treated subjects resolved without intervention during continued

treatment. The following is a description of adefovir treated subjects who experienced hepatic AEs:

- One subject (7−11 years, male) experienced Grade 3 ALT elevation, Grade 2 AST elevation, Grade 1 GGT and alkaline phosphatase elevations at Week 48. At post Week 48 evaluations, the subject's serum ALT normalized.

- A male subject in the 12−17 years group had a treatment related Grade 3 ALT concentration, Grade 2 AST abnormality and Grade 1 GGT abnormality at Week 48. The subject's serum ALT value decreased to Grade-1 laboratory abnormality at the post blinded therapy period.

- A female subject (2−6 years) had a treatment-related SAE of Grade-3-4 hepatic enzyme increased ("elevated liver enzymes") at Week 48 (confirmed at a retest 2 days later). This event was also considered severe hepatic flare. Her baseline ALT values were Grade 2. Data from the open-label treatment shows the subject's serum ALT value has decreased to Grade 1 laboratory abnormality.

- Lastly, a female subject (2−6 years) had a Grade-1 non-serious AE of hepatomegaly from Week 42 to 46. The event was judged to be unrelated to study treatment and resolved without intervention. No significant changes in hepatic transaminases, prothrombin time, total or direct bilirubin, or serum albumin was noted during the event.

In the placebo group, three subjects had hepatic AEs- increased ALT (Grade 4 SAE) one subject; hepatitis "hepatic flare" (Grade 1) one subject; and hepatitis "severe hepatic flare" (Grade 3) one subject.

Severe Hepatic Flares
Three adefovir treated subjects had ALT elevations that met the definition of a severe hepatic flare. One of these subjects was also reported as having a treatment-related Grade-3 SAE that resolved during continued adefovir treatment. These flares were not associated with concomitant changes in laboratory parameters (total bilirubin >2.5mg/dL or 1.0mg/dL above baseline, albumin <3.0g/dL) suggesting worsening hepatic function. None of the hepatic flares were associated with hepatic decompensation, and none resulted in interruption or discontinuation of study treatment.

Post-treatment Exacerbation of Chronic Hepatitis B
Three subjects discontinued treatment prior to Week 48. None experienced a post-treatment exacerbation of CHB infection. Ten subjects (6%) had post-treatment exacerbation of CHB (without changes in bilirubin or albumin) during the open label treatment period. Please refer to the Safety Profile during the Open Label Treatment Period section for details. In the adult studies, up to 25% of subjects experienced post-treatment exacerbation of CHB after discontinuation of treatment. This information is already included in the product's label.

Psychiatric Adverse Events
Four (4%) of the adefovir treated subjects had psychiatric AEs. All were Grade 1 or 2. With the exception of one subject, none of the AEs reported in the 3 subjects were serious. The AEs were: adjustment disorder (one subject), insomnia (one subject), and depression (one subject). The subject with the depression AE had history of ADHD and was on treatment with Adderall and methylphenidate HCL. The subject who experienced the SAE ('worsening of behavioral disorder') was discussed in the SAEs section.

No psychiatric AEs were reported from the placebo arm.

Rash
Three subjects in the adefovir arm had urticaria reported as AEs. One was considered to be treatment related (Grade 2) and resolved with medication. Treatment with adefovir was not interrupted or discontinued. None were severe or serious.

In addition to urticaria, one subject had a treatment-related Grade-1 'rash' which was treated and one subject had treatment-related Grade-1 pruritus which resolved without intervention.

Adverse Events Related to Appetite
In the adefovir group, 8 subjects were reported to have AEs related to appetite or weight loss. Five subjects were reported to have "anorexia" and 2 subjects were reported to have "decreased appetite". Of these, one subject experienced weight decrease, which resolved without intervention. When combined the number of subjects with appetite related AEs increases to 6%. All events were Grade 1 and no intervention was required. Two of the events were considered treatment-related.

In the placebo group, no subject experienced anorexia or decreased appetite.

Laboratory Findings

It is difficult to determine the absolute contribution of adefovir to laboratory abnormalities because the disease itself can lead to laboratory abnormalities. However, having a placebo comparator arm does help to ascertain cause of laboratory abnormalities. The following is an evaluation of potential adefovir-related laboratory abnormalities that were reported in the pediatric trial.

Renal
The median serum creatinine concentrations were the same in the adefovir and placebo treatment groups at baseline and were unchanged after 48 weeks of blinded treatment (0.6 mg/dL in both groups at both assessment times).

In each of the age/treatment subgroups receiving adefovir, median serum creatinine increased by 0.1 mg/dL from baseline to Week 48; in the age/treatment subgroups receiving placebo, the increase in median serum creatinine from baseline to Week 48 varied between 0 and 0.2 mg/dL.

Tables 27 and 28 summarize these findings.

Table 27: Serum Creatinine values Applicant's Analyses

Serum Creatinine (mg/dL)	2−6 Years a		7−11 Years a		12−17 Years a		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Baseline								
Mean (SD)	0.3 (0.09)	0.4 (0.05)	0.5 (0.11)	0.6 (0.10)	0.7 (0.13)	0.7 (0.20)	0.6 (0.19)	0.6 (0.18)
Median	0.3	0.4	0.5	0.6	0.7	0.6	0.6	0.6
95% CI	0.3, 0.4	0.4, 0.4	0.5, 0.5	0.5, 0.6	0.7, 0.7	0.6, 0.8	0.5, 0.6	0.5, 0.6
Q1, Q3	0.3, 0.4	0.4, 0.4	0.4, 0.6	0.5, 0.6	0.6, 0.8	0.5, 0.8	0.4, 0.7	0.4, 0.7
Min, Max	0.2, 0.5	0.3, 0.5	0.2, 0.7	0.3, 0.7	0.4, 1.1	0.4, 1.3	0.2, 1.1	0.3, 1.3
Week 48								
Mean (SD)	0.4 (0.08)	0.5 (0.07)	0.6 (0.10)	0.6 (0.07)	0.8 (0.13)	0.8 (0.16)	0.6 (0.19)	0.6 (0.17)
Median	0.4	0.5	0.6	0.6	0.8	0.8	0.6	0.6
95% CI	0.4, 0.4	0.4, 0.5	0.5, 0.6	0.5, 0.6	0.7, 0.8	0.7, 0.8	0.6, 0.7	0.6, 0.7
Q1, Q3	0.3, 0.4	0.4, 0.5	0.5, 0.6	0.5, 0.6	0.7, 0.9	0.6, 0.9	0.5, 0.8	0.5, 0.8
Min, Max	0.3, 0.6	0.4, 0.6	0.4, 0.8	0.5, 0.7	0.5, 1.0	0.5, 1.1	0.3, 1.0	0.4, 1.1

Table 28: Calculated Creatinine Clearance Applicant's Analyses

Calculated Creatinine	2−6 Years a		7−11 Years a		12−17 Years a		Total	
Clearance (mL/min/1.73 m2)	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Baseline								
Mean (SD)	179.6 (48.20)	146.7 (22.59)	160.7 (42.31)	142.9 (24.84)	157.5 (26.55)	168.9 (39.32)	162.9 (37.55)	155.8 (33.94)
Median	162.3	152.0	149.6	137.8	152.4	164.5	154.0	150.7
95% CI	159.9, 199.3	134.0, 159.5	146.9, 174.6	131.7, 154.1	150.5, 164.4	154.0, 183.7	156.1, 169.8	147.1, 164.5
Q1, Q3	137.5, 209.0	131.2, 157.4	132.5, 176.5	129.3, 151.8	141.0, 174.8	144.8, 193.9	139.3, 180.1	136.1, 168.0

Min, Max	118.8, 286.6	110.6, 195.8	116.0, 347.9	107.6, 219.3	109.3, 253.4	95.0, 293.1	109.3, 347.9	95.0, 293.1
Week 48								
n	**21**	**12**	**36**	**18**	**51**	**27**	**108**	**57**
Mean (SD)	154.2 (26.42)	138.6 (21.32)	143.8 (24.72)	143.9 (15.69)	144.6 (23.08)	154.7 (30.04)	146.2 (24.39)	147.9 (25.07)
Median	148.5	132.8	140.5	142.6	142.5	151.8	145.3	149.6
95% CI	142.9, 165.5	126.6, 150.7	135.7, 151.9	136.7, 151.2	138.3, 151.0	143.4, 166.0	141.6, 150.8	141.4, 154.4
Q1, Q3	138.9, 170.5	123.1, 159.1	128.1, 157.9	133.8, 151.3	125.9, 163.0	127.9, 171.5	129.3, 163.3	129.8, 161.5
Min, Max	105.0, 209.9	104.1, 171.6	90.7, 202.1	112.8, 174.4	95.9, 204.6	105.8, 211.2	90.7, 209.9	104.1, 211.2

Based on this reviewer's analyses, treatment-emergent graded laboratory abnormalities in serum creatinine occurred in 19% (22/115) of the adefovir treated subjects and in 24% (14/58) of the placebo treated subjects. All graded laboratory abnormalities for creatinine were Grade 1. The Sponsor reports that there were 16% treatment-emergent graded serum creatinine abnormalities in the adefovir arm and 10% in the placebo arm (all Grade 1). The difference between this reviewer's analyses and the Applicant's is due to the definition of change in a laboratory safety parameter. A confirmed change in a laboratory safety parameter was defined by the Applicant as change that occurs in two consecutive measurements. Only subjects with confirmed change in a laboratory values were reported by the Applicant as having laboratory adverse events.

No subject had a confirmed increase of at least 0.5 mg/dL from their baseline serum creatinine concentration. One subject had a confirmed increase of at least 0.3 mg/dL (adefovir treated subject 12−17 years, male). This subject had a creatinine concentration of 0.7 mg/dL at baseline. At Week 4, he had a serum creatinine concentration of 1.1 mg/dL (Grade 1), with varying values during weeks 8 to 36 between 0.8 mg/dL and an isolated measurement of 1.0 mg/dL (Week 12). At Week 36, concentration returned to 1.0 mg/dL and remained there at Weeks 44 and 48. There were no associated AE reported with the increase in serum creatinine. In the open-label treatment follow-up period, creatinine was 1.1 mg/dL at 2 subsequent assessments. His serum phosphorus concentration was 4.1 mg/dL at baseline and ranged between 3.3 and 5.8 mg/dL during the first 48 weeks of adefovir treatment (and between 3.3 and 4.5 mg/dL in the open-label treatment period).

Many subjects were noted to have increase in their creatinine by at least 0.2 mg/dL from baseline (non-confirmed – i.e. not necessarily seen in two consecutive measurements). However, the increase did not automatically lead to a Grade 1 laboratory abnormality. Twenty percent (23/115) of the adefovir treated subjects had increased creatinine by at least 0.2 mg/dL during the blinded study period. Thirty percent (35/115) had a similar increase seen during the open treatment period. For the placebo treated group, 21% (12/58) had increased creatinine by at least 0.2 mg/dL during the blinded study period and 26% (15/58) had increased creatinine during the open treatment period.

In evaluating the adefovir treated group, Grade 3 and 4 laboratory abnormalities were seen for calcium, phosphorus and sodium. Overall, there were 3 subjects (2%) with Grade 3 toxicity in these chemistry laboratories. All were Grade 3 events.

- One subject (2-6 years, female) had Grade 3 hypercalcemia (12mg/dL Week 48). Post Week 48 data showed her calcium concentration had returned to the normal range. This subject also had report of Grade 3 hypernatremia. Her baseline creatinine was 0.2mg/dL and the highest recorded post baseline creatinine level was 0.4mg/dL (up to week 72).

- One subject had an abnormality in serum phosphorus. Subject (12−17 years, male) had his phosphorus concentration decreased to 1.9 mg/dL (Grade-3). His serum phosphorous increased to 2.1 mg/dL (Grade-2) in a retest 6 days later. At Week 48 it was 3.1 mg/dL (Grade-1). Adefovir treatment was not interrupted, and the subject received no supplementation. His baseline serum creatinine was 0.8 mg/dL; the highest recorded value during the blinded phase was 0.9mg/dL (Week 36). The highest overall recorded value was 1.0 mg/dL (Grade 1) at Week 84 (post blinded phase of study). No subject had a confirmed serum phosphorus concentration less than 2 mg/dL.

- One subject (7−11 years, female) had a serum sodium concentration of 150 mEq/L (Grade-3) at Week 48. During the open-label treatment period, her serum sodium concentration had returned to the normal range and remained normal through Week 84. Her creatinine value remained with in the normal range. Table 29 summarizes the Grade 3-4 renal (chemistry) laboratory abnormalities.

Table 29: Grade 3-4 Renal Laboratory Toxicity

	2-<7 years		7-<12		12-<18		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Hypercalcemia	1 (4%)	0	0	0	0	0	1 (< 1%)	0
Hypernatremia	1 (4%)	1 (8%)	1 (3%)	1 (5%)	0	0	2 (2%)	2 (3%)
↓Phosphorus	0	0	0	0	1 (2%)	0	1 (< 1%)	0

Hepatic

A smaller percentage of subjects in the adefovir group (8%, 9/115) had Grade-3 or 4 abnormalities in serum ALT compared with the placebo group (21%, 12/58). Of the nine adefovir treated subjects who had treatment-emergent Grade-3 (n = 6) or Grade-4 (n = 3) abnormalities in serum ALT, two had significant abnormalities (discussed below).

Of the remaining seven subjects, three had Grade-2 ALT abnormalities at screening and/or baseline, sporadic Grade-1 and/or Grade-2 abnormalities and a single Grade-3 abnormality early in treatment (≤ Week 8). ALT value decreased as treatment continued. The other 4 subjects all had graded ALT abnormalities at screening and baseline and had more frequent on-treatment Grade-3 or 4 abnormalities in serum ALT.

Significant hepatic laboratory abnormalities (increase to Grade 3 or 4 from normal baseline value or increase to Grade 4 from Grade 1 baseline value) occurred in 2 adefovir treated subjects. One subject (2−6 years, male) had graded abnormalities in ALT at the majority of assessment times, including screening (Grade-2) and baseline (Grade 1). His ALT increased to Grade-4 abnormality at Week 36. At retest a month after, his ALT decreased to Grade-3 abnormality, and it continued to decrease, falling below the baseline value at Week 44 and Week 48 (24 U/L). The subject also had sporadic graded elevations in AST, which followed the same trend as ALT. Another subject (7−11 years, male) had a serum ALT concentration increased to Grade-3 abnormality at Week 48. The subject's ALT concentration had normalized during the open- label treatment period. The event resolved without intervention. This subject also had sporadic graded elevations in serum AST, including a Grade-2 abnormality at Week 48. Table 30 summarizes the Grade 3-4 laboratory abnormalities.

Table 30: Grade-3 or 4 abnormalities Applicant's Analyses

Laboratory Parameter with a Grade-3 or 4 Abnormality a (n, %)	2−6 Years		7−11 Years b		12−17 Years b		Total	
	ADV (n=23)	PLB (n=12)	ADV (n=36)	PLB (n=19)	ADV (n=56)	PLB (n=27)	ADV (n=115)	PLB (n=58)
Serum Chemistry								
ALT	3 (13%)	4 (33%)	5 (14%)	4 (21%)	1 (8%)	4 (15%)	9 (8%)	12 (21%)
AST	0	2 (17%)	2 (6%)	0	1 (2%)	1 (4%)	3 (3%)	3 (5%)
Bilirubin, Total	0	0	0	0	0	1 (4%)	0	1 (2%)
Prothrombin Time	0	0	1 (3%)	0	0	0	1 (< 1%)	0

Vital Signs

In general, there were no significant changes in vital signs identified.

Human Carcinogenicity

The non-clinical carcinogenicity studies have demonstrated that adefovir is not carcinogenic.

Withdrawal Phenomena and/or Abuse Potential

There is no withdrawal phenomenon or abuse potential with adefovir.

Human Reproduction and Pregnancy Data

Adefovir is classified as Pregnancy Category C. There are no adequate and well controlled studies on use of adefovir during pregnancy. To monitor fetal outcomes of pregnant women

exposed to adefovir, a pregnancy registry has been established, and healthcare providers are encouraged to register patients; this is already included in the Hepsera tablet label.
During the blinded study period, one subject discontinued treatment due to non-compliance (subject did not show up for numerous visits). A short narrative for this subject is as follows: 'Adefovir-dipivoxil–treated subject (12−17 years) received 10 mg of adefovir dipivoxil once daily from 22 November 2004 through 08 May 2005. On an unknown date, the subject's mother called the study site to report that the subject was "about 8 weeks pregnant." The investigator estimated that the subject became pregnant some time in . The subject was lost to follow-up, never returning to the study center after the pregnancy was reported, and neither the investigator nor Gilead received laboratory test results confirming the pregnancy. The outcome of the pregnancy is not known. The subject was permanently discontinued from the study on 01 August 2005; the primary reason given by the investigator was "subject noncompliance" '.

Assessment of Effect on Growth

No effect on growth was noted after administration of adefovir for 48 weeks.

Safety Profile during Open Label Treatment Period

A total of 162 subjects entered the open label treatment period [33 subjects (97%) from cohort 1, 54 subjects (98%) from cohort 2 and 75 subjects (94%) from cohort 3). Nine subjects discontinued from the study by the time of the data cut-off for this study update. Reasons for discontinuation included persistent viremia, enrollment into another investigational study, AE (depression), noncompliance, and withdrawal of consent due to relocation. The median exposure to adefovir was 72 weeks for cohort 1 and 96 weeks for cohorts 2 and 3.

The common adverse events reported in this open label treatment period were similar (in types and frequencies) to the ones reported during the first 48 weeks of the study.

Severe AEs were also comparable between the two periods. Treatment related severe AE of hepatitis was reported slightly more frequently (2%) during the open label period when compared to the double blind treatment period (0%). In addition, two subjects were reported to have depression (severe AE) during the open label treatment period.

The SAEs profiles were comparable between the two treatment periods, except for depression. There were 2 subjects (1%) with depression reported as SAE. One of these subjects had a history of depression and suicidal statements and a prior diagnosis of 'adaptive disorder. This subject experienced treatment-related depression and permanently discontinued from the study. The second subject also had history of depression and self-inflicted wounds. He had Grade 3 SAE of alcohol poisoning and depression, considered unrelated to treatment. Treatment with adefovir was not interrupted.

Hepatic adverse events were reported in 4% of the subjects during the open label period (compared to 3% during the double blind treatment period). Grade 3, 4 and marked hepatic laboratory abnormalities were also similar between the two treatment periods.

Severe hepatic flare was reported in 3 subjects during the double blind treatment period. During the open label period, one subjects had severe hepatic flare considered an SAE. The event occurred 3 months after discontinuation of adefovir (due to depression). No changes in total bilirubin or albumin were reported. In addition, after the data cut-off for this update, 9 subjects (4 of whom received the tablet formulation) were reported to have post-treatment exacerbations (SAE) of hepatitis B. None had concomitant changes in total bilirubin or albumin.
No renal adverse events were reported during the open label period. There was no confirmed serum creatinine increase of ≥ 0.5mg/dL and no AEs was reported for changes in phosphorus.

There were no deaths reported during this study period.

Overdose Experience

The Hepsera® labeling describes gastrointestinal side effects after administration of adefovir 500mg daily for 2 weeks and 250mg daily for 12 weeks. If overdose occurs, monitoring for toxicity should occur. Hemodialysis removes approximately 35% of a 10 mg single dose of adefovir.

Post marketing Experience

Adefovir has been marketed for treatment of CHB infection in adults in the US since 2002 as Hepsera® tablet. No new safety signals have been identified in adult patients.

Adequacy of Patient Exposure and Safety Assessments

The Applicant submitted safety data on 173 patients between 2 and 18 years of age who received Hepsera® oral suspension or tablet for at least 48 weeks and up to 144 weeks. The number of pediatric patients and duration of treatment with adefovir represents adequate database upon which to determine safety and efficacy for the proposed dose that will be included in the label. The study type, design, demographics, extent of exposure, postmarketing experience, adequacy of clinical experience, and clinical testing have been summarized above, and support the safety findings.

8. ADDITIONAL CLINICAL ISSUES

Dosing Regimen and Administration

The Applicant proposed the following dosing regimens of Hepsera® tablet in pediatric patients:

- Pediatric patients (12-<18 years of age): One 10mg tablet once daily.

The Applicant's proposal excludes dosing in the younger age group (2-<12 years of age). However, recent legislation regarding pediatric drug development recommend that although no dosing and administration will be available for pediatric patients (2-<12 years), information from this sNDA including data on efficacy and PK should be included in the approved labeling.

Drug-Drug Interactions
Drug-drug interactions have been characterized and important interactions are included in the Hepsera® tablet label.

Special Populations
Adefovir is renally excreted. Therefore, renal impairment can impact the pharmacokinetics of adefovir. A pharmacokinetic study evaluating adefovir suspension in adults with mild, moderate and severe renal impairment was submitted and reviewed under NDA (21-449 SN 000). No additional benefits were seen from administration of the suspension formulation when compared to the tablet formulation. Therefore, no new recommendations (changes in labeling) were made for adults with renal impairment.

Pediatrics
This is a pediatric sNDA and the above information applies to pediatric patients.

Postmarketing Risk Management Plan
Adefovir has been marketed in the US since 2002. No post-marketing safety issues have been identified.

9. OVERALL ASSESSMENT

Conclusions

Based on the safety, pharmacokinetic and antiviral activity reviewed in this NDA, the application is recommended for approval. Clinical pharmacokinetic, safety and efficacy data from 173 pediatric patients with CHB infection aged 2 to 18 years treated with Hepsera® oral suspension or tablet for 48 weeks demonstrated comparable exposures (e.g., AUC) at the doses studied and general safety profile.

However, efficacy (proportion of subjects with HBV DNA <1000 copies/mL plus normalization of ALT) was demonstrated for the overall adefovir treated group and more specifically in the oldest age group (12-<18 years) when compared to placebo. Therefore, there will be no treatment recommendation for patients < 12 years of age. Although adefovir does not appear to have very potent activity against hepatitis B in pediatric patients, Hepsera® 10mg tablet should be approved for use in patients 12-<18 years of age as it provides an alternative treatment for pediatric patients who currently have very limited FDA approved treatment options.

Recommendation on Regulatory Action

From a clinical perspective, the NDA for Hepsera® tablet use in children 12-<18 years of age should be approved. Based on data included in this sNDA, Hepsera® should not be used in patients <12 years of age.

Recommendation on Postmarketing Actions

The PMC was issued for two pediatric categories: birth to <2 years of age and >2 to <18 years of age. There are no outstanding postmarketing actions remaining for the older than 2 years old group. No studies have been performed on subjects less than 2 years of age. When the PMC was initially issued, conduction of a study in the <2 years old age group was included in hopes of providing a public health benefit for this age group should the natural history of the disease becomes more understood and consensus becomes established on treatment benefit for this younger age group. Based on the review of literature, children younger than 2 years of age are rarely treated for CHB infection. Therefore, it is the Division's recommendation that the study requirement for this age group be waived.

Risk Management Activity

The current labeling of Hepsera® adequately describes the Warnings, Contraindications and Precautions related to adefovir. As such, no additional post-approval risk management activities are required.

Required Phase 4 Commitments

There are no new required Phase 4 requests.

Other Phase 4 Requests

There are no additional Phase 4 requests.

Labeling Review

The Hepsera® tablet label will be revised to include salient information about its use in the pediatric population, including pediatric pharmacokinetic, efficacy and safety data.

10. REFERENCES

1. Jonas, MM. Treatment of Chronic Hepatitis B in Children. *Journal of Pediatric Gastroenterology and Nutrition 2006; 43:s56-60.*

2. Shneider, BL, Gonzalez-Peralta, R, Roberts EA. Controversies in the Management of Pediatric Liver Disease: Hepatitis B, C and NAFLD: Summary of a Single Topic Conference. *Hepatology* 2006;44:1344-1354

Additional Literature

Dikici B. et al. Therapeutic Vaccination in the Immunotolerant Phase of Children with Chronic Hepatitis B Infection. *PIDJ;* 2003;22:345-349

D'Antiga L. et al. Combined Lamivudine/Interferon- α Treatment in Immunotolerant Children Perinatally Infected with Hepatitis B: A Pilot Study. *The Journal of Pediatrics* 2006;148:228-33

FDA/CDER NDA 21-449/S-006 Hepsera Medical Review

FDA/CDER NDA 21-003/SE1-002 and NDA 21-004/SE1-002 Epivir-HBV Medical Review

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yodit Belew
12/19/2007 06:34:23 AM
MEDICAL OFFICER

Linda Lewis
12/19/2007 10:45:28 AM
MEDICAL OFFICER