U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21449/SE5-011
Drug Name:	Hepsera® (Adefovir Dipivoxil)
Indication(s):	Chronic hepatitis B in patients with less than 18 years old
Applicant:	Gilead
Date(s):	Submission date: 06/22/07
	PDUFA date: 12/25/07
Review Priority:	Priority
Biometrics Division:	DB4
Statistical Reviewer:	Karen Qi, PhD
Concurring Reviewers:	Greg Soon, PhD
Medical Division:	Division of Antiviral Products (DAVP)
Clinical Reviewer:	Yodit Belew, MD
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Keywords: clinical study, NDA review, one study application, pediatric exclusivity, Fisher's exact test

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The 10 mg tablet formulation of adefovir dipivoxil (Hepsera®) was approved in the United States for the treatment of chronic hepatitis B (CHB) in adult patients in September 2002. In current supplement NDA (sNDA), the sponsor submitted the 48-week data from Study GS-US-103-0518, a phase III, randomized, double-blind study evaluating the efficacy and safety of adefovir dipivoxil in pediatric patients. In the study, the adefovir oral suspension was used in subjects with 2–11 years of age, and the marketed 10-mg adefovir tablet was used in subjects with 12–17 years old. The sponsor intended to seek the Agency's approval of an indication of use of the 10-mg adefovir tablet in the adolescent patients (patients age 12 to 17 years).

After reviewing the 48-week efficacy results for the phase III trial, the statistical reviewer concluded that overall adefovir dipivoxil provided statistical evidence of superior efficacy to the placebo with respect to the primary efficacy endpoint: the proportion of subjects with HBV DNA < 1000 copies/mL and normal ALT at Week 48. Furthermore, the superior efficacy of adefovir was shown in the 12–17–year age group, but not in the 2–6–year or 7–11–year age group.

1.2 Brief Overview of Clinical Studies

This review report focus on evaluating the 48-week efficacy results for Study GS-US-103-0518. The study was a Phase 3, double-blind, multicenter, multinational trial. The primary objective of the study was to investigate the efficacy of adefovir dipivoxil for the treatment of chrnonic hepatitis B in children and adolescents (age 2 to < 18) compared to placebo following 48 weeks of treatments. The study was conducted in 26 centers in USA and five counties in Europe. A total of 173 subjects was randomized in a 2:1 ratio to either receive adefovir (n=115) or placebo (n=58). The randomization was stratified by the age at the first dose of study treatment (2 to < 7 years; >= 7 to < 12 years; >= 12 to < 18 years) and prior treatment for CHB (prior treatment; no prior treatment). Subjects in 2 to 6 years of age received adefovir or placebo as an oral suspension formula at a dose of 0.3 mg/kg; subjects >= 7 to < 12 years of age received adefovir or placebo as an oral suspension formula at a dose of 0.25 mg/kg; and subjects >=12 to < 18 years of age received adefovir 10 mg or placebo as a tablet. During the initial 48 weeks, the study was double-blind and the subjects were supposed to received the randomly assigned medication. At the end of double-blind treatment, adefovir-treated subjects and those placebo-treated subjects who did not exhibit HBeAg or HBsAg seroconversion at Week 44 were offered the opportunity to enter an open-label adefovir treatment lasting up to 240 weeks. The primary efficacy endpoint was the proportion of subjects with serum HBV DNA < 1000 copies/mL (PCR based assay) and normal ALT at Week 48.

1.3 Statistical Issues and Findings

Upon the submitted data, the reviewer found that the sponsor did not regard ALT as normal when it equaled to 1 x upper normal limit (UNL), which was different from what is recommended in Johns Hopkins Harriet Lane Handbook (16th edition). Nevertheless, the different definition of normal ALT

led to slightly different results for the primary efficacy endpoint and some ALT-related secondary efficacy endpoints, and did not affect the overall conclusion.

Furthermore, upon consultant with the medical reviewer, Dr. Belew, adefovir is expected to have an effect directly on HBV and should work similarly regardless of age since it is not an immune modulator. The baseline ALT level instead of the age could play a more significant role on determining whether the subject is likely to respond to the treatment. The reviewer conducted an analysis in the subgroup of subjects with baseline ALT > 2xUNL, the criteria frequently used in practice to determine whether the subjects should receive a treatment. The analysis results revealed that overall the adefovir group had significantly greater percentage of patients having HBV DNA < 1000 copies/mL and normal ALT at Week 48 than the placebo group (adefovir: 21%, placebo: 0%; p-value based on Fisher's exact test = 0.005). The reviewer further performed the subgroup analysis with respect to the age among these subjects with baseline ALT > 2xUNL, and found that more adefovir-treated subjects than the placebo-treated subjects achieved the primary endpoint in each individual age group, but the treatment difference was insignificant in all three age groups.

Also, since the subjects in both 2–6–year and 7–11–year groups received the investigational suspension formulation and the subjects in the 12–17–year group received the tablet formulation, the reviewer performed the analysis to evaluate the treatment effect in each of the two formulations as measured by the primary efficacy endpoint. The group using tablet formulation was essentially the same as the 12–17–year group, and the treatment difference was significant (adefovir: 23%, placebo: 0%, p-value based on Fisher's exact test = 0.007). In the group using the investigational suspension formulation, 17% of adefovir-treated subjects achieved the primary efficacy endpoint compared with 3% of placebo-treated subjects, and the treatment difference was not significant.

Finally, the subgroup analysis with respect to gender revealed that the treatment effect was different between female and male subjects. The p-value based on the Breslow-Day test for the homogeneity of the odds ratios for the two gender groups was 0.034. Overall, among the female subjects, there was no obvious treatment difference in spite that more adefovir-treated subjects achieved the primary endpoint compared with placebo-treated subjects (adefovir: 10%, placebo: 5%); but the treatment difference was apparent among the male subjects (adefovir: 26%, placebo 0%).

2. INTRODUCTION

2.1 Overview

The 10 mg tablet formulation of adefovir dipivoxil was approved in the United States for the treatment of CHB in adult patients. The current supplement sNDA contained the 48-week data from a phase III, randomized, double-blind study evaluating the efficacy and safety of adefovir dipivoxil in pediatric patients. In the study, the adefovir oral suspension was used in subjects with 2–11 years of age, and the marketed 10-mg adefovir tablet was used in subjects with 12–17 years old. The sponsor intended to seek the Agency's approval of an indication of use of 10-mg adefovir tablet in the adolescent patients (patients age 12 to 17 years). This review report focus on evaluating the 48-week efficacy results for the study.

2.2 Data Sources

The application was paper submission, but the data can be found in FDA internal network drive of [redacted]

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The study was a Phase 3, double-blind, multicenter, multinational trial. The primary objective of the study was to investigate the efficacy of adefovir dipivoxil for the treatment of chrnonic hepatitis B in children and adolescents (age 2 to < 18) compared to placebo following 48 weeks of treatments. The study was conducted in 26 centers in six counties. A total of 173 subjects was randomized in a 2:1 ratio to either receive adefovir (n=115) or placebo (n=58). The randomization was stratified by the basis of age at the first dose of study treatment (2 to < 7 years; >= 7 to < 12 years; >= 12 to < 18 years) and prior treatment for CHB (prior treatment; no prior treatment). Subjects in 2 to 6 years of age received adefovir or placebo as an oral suspension formula at a dose of 0.3 mg/kg; subjects >= 7 to < 12 years of age received adefovir or placebo as an oral suspension formula at a dose of 0.25 mg/kg; and subjects >=12 to < 18 years of age received adefovir 10 mg or placebo as a tablet.

During the initial 48 weeks, the study was double-blind and the subjects were supposed to received the randomly assigned medication. The HBV DNA and ALT were assessed at Weeks 4, 8, 12, 24, 36, 44 and 48; while hepatitis B serology was measured at Weeks 12, 24, 36, 44 and 48. At the end of double-blind treatment, adefovir-treated subjects and those placebo-treated subjects who did not exhibit HBeAg or HBsAg seroconversion at Week 44 were offered the opportunity to enter an open-label adefovir treatment lasting up to 240 weeks.

The primary efficacy endpoint was the proportion of subjects with serum HBV DNA < 1000 copies/mL (PCR based assay) and normal ALT at Week 48. The secondary efficacy endpoints included the following parameters:

- serum HBV DNA < 1000 copies/mL and normal ALT at Weeks 96, 144, 192 and 240
- change from baseline in serum HBV DNA
- change from baseline in ALT
- normal ALT at Weeks 96, 144, 192 and 240
- serum HBV DNA < 1000 copies/mL, normal ALT and HBeAg seroconversion for subjects who were HBeAg positive at baseline
- HBeAg loss (HBeAg negative) and/or HBeAg seroconversion (HBeAg negative, HBeAb positive) for subjects with HBeAg positive at baseline
- HBsAg loss (HBsAg negative) and/or HBsAg seroconversion (HBsAg negative, HBsAb positive) for subjects with HBsAg positive at baseline
- durability of HBeAg seroconversion or HBsAg seroconversion

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

Table 1 shows subject disposition by age and treatment group. Of the 293 subjects who were screened, 173 were randomized and treated (115 in adefovir group, 58 in placebo group). All placebo-treated subjects completed 48 weeks of double-blind treatment, as did 112 (97%) of the 115 adefovir-treated subjects. The three subjects who discontinued prematurely were in the 12–17–year adefovir group: one subject was withdrawn from the study because of AEs, and two subjects were withdrawn because of noncompliance.

Table 1: Subject Disposition by Age and Treatment Group (All Treated)

	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)**
Randomized and treated	23	12	36	19	56	27	115	58
Completed blinded 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
Subject noncompliance	0	0	0	0	2 (4%)	0	2 (2%)	0

Source: Study GS-US-103-0518 Interim Clinical Study Report, Section 6, Table 6-1.

Table 2 below displays the demographics and selective baseline characteristics. Demographics were balanced between the two treatment groups. A majority of the subjects was male (65%) and white (64%). The mean age was 11 (±4) years old. The most common HBV genotypes were A (48%) and D (28%). The proportion of subjects with prior CHB treatment, baseline HBV DNA and ALT level were similar between the two groups, while slightly more percentage of subjects having abnormal ALT in adefovir group than that in the placebo group. Most subjects had positive HBe antigen and all patients had positive HBs antigen.

Table 2: Demographics and Selected Baseline Characteristics (All Treated)

	Adefovir (n=115)	Placebo (n=58)	Total (n=173)
Sex – n (%)			
Female	41 (36)	19 (33)	60 (35)
Male	74 (64)	39 (67)	113 (65)
Race – n (%)			
White	70 (61)	41 (71)	111 (64)
Asian	29 (25)	12 (21)	41 (24)
Black	11 (10)	3 (5)	14 (8)
Other	5 (4)	2 (3)	7 (4)
Age			
Mean (SD)	11 (4)	11 (4)	11 (4)
Median	11	11	11
Q1, Q3	7, 14	8, 14	8, 14
Min, Max	2, 17	2, 17	2, 17
HBV genotype – n (%)			
A	51 (44)	32 (55)	83 (48)
B	13 (11)	5 (9)	18 (10)
C	10 (9)	4 (7)	14 (8)
D	35 (30)	14 (24)	49 (28)
E	3 (3)	2 (3)	5 (3)
F	2 (2)	0 (0)	2 (1)
Not done	1 (1)	1 (2)	2 (1)
Piror CHB treatment – n (%)			
Yes	64 (56)	33 (57)	97 (56)
No	51 (44)	25 (43)	76 (44)
HBV DNA (log_{10} copies/mL)			
Mean (SD)	8.74 (0.89)	8.67 (1.02)	8.71 (0.93)
Median (Q1, Q3)	8.84 (8.37, 9.26)	8.78 (8.39, 9.33)	8.80 (8.39, 9.30)
ALT as multiple of ULN			
Mean (SD)	2.9 (2.0)	2.6 (1.4)	2.8 (1.8)
Median (Q1, Q3)	2.3 (1.5, 3.4)	2.2 (1.6, 3.5)	2.3 (1.5, 3.4)
ALT – n (%)			
Normal	8 (7)	2 (3)	10 (6)
Abnormal	107 (93)	56 (97)	163 (94)
HBeAg – n (%)			
Negative	2 (2)	1 (2)	3 (2)
Positive	113 (98)	57 (98)	170 (98)
HBeAb – n (%)			
Negative	0 (0)	0 (0)	0 (0)
Positive	2 (2)	1 (2)	3 (2)
Not done	113 (98)	57 (98)	170 (98)
HBsAg – n (%)			
Negative	0 (0)	0 (0)	0 (0)
Positive	115 (100)	58 (100)	173 (100)
HBsAb – n (%)			
Negative	0 (0)	0 (0)	0 (0)
Positive	0 (0)	0 (0)	0 (0)
Not Done	115 (100)	58 (100)	173 (100)

Source: Study GS-US-103-0518 Interim Clinical Study Report, Section 6, Tables 6-3 and 6-4.

3.1.3 Statistical Methodologies

The efficacy analyses were conducted on the randomized subjects who received at least one dose of study medication. The measurements closest to the first day when the subject received the study medication were regarded as baseline values. For the visits after baseline, the mid-point between two consecutively scheduled visits was used as the dividing point for the visit window for each visit. The primary efficacy endpoint was the proportion of subjects with both HBV DNA < 1000 copies/mL and normal ALT at Week 48. If either endpoint was missing a Week 48 value, the Week 44 value was carried forward and used in the combined endpoint. If a subject did not have a serum HBV DNA value at both Weeks 44 and 48 or an ALT value at both Weeks 44 and 48, the that subject was considered as a failure for the primary efficacy analysis. The Fisher exact test was performed to compare the treatment difference for the primary endpoint. The primary endpoint was also summarized by the age group. Similar approach was applied for the secondary efficacy endpoints with binary outcome. In regards to the secondary efficacy variables with continuous outcome, the mean, standard deviation and 95% confidence intervals for the treatment difference were calculated.

3.1.4 Sponsor's Results

Table 3 shows the sponsor's analysis results for the primary endpoint. According to the sponsor, the adefovir group had the significantly higher proportion of subjects achieving HBV DNA < 1000 copies/mL and normal ALT at Week 48 than the placebo group (adefovir: 19%, placebo: 2%, p-value based on Fisher's exact test < 0.001). Furthermore, the sponsor demonstrated that the treatment difference was insignificant in the 2–6 or 7–11–year age groups, but was significant in the 12–17–year age group.

Table 3: Sponsor's Results for Primary Efficacy Endpoint – Subjects with HBV DNA <1000 copies/mL and normal ALT at Week 48 (all treated)

	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%)	1 (8%)	6 (17%)	0 (0%)	13 (23%)	0 (0%)	22 (20%)	1 (2%)
p-value based on Fisher's exact test	1.000		0.083		0.007		<0.001	

Source: Study GS-US-103-0518 Interim Clinical Study Report, Section 7, Table 7-1.

Additionally, the sponsor's analyses for the secondary endpoints revealed that the overall the adefovir was superior to the placebo for most of the key secondary endpoints except for loss of HBeAg and HBeAg seroconversion. Similar to the primary efficacy analysis, the sponsor further showed that the treatment differences in most of key secondary endpoints were significant in the 12–17–year age group, but not significant in the 2–6 or 7–11–year age groups. Specifically,

1. Overall, the difference between the two treatment groups in the mean change from baseline to Week 48 in HBV DNA (log10 copies/mL) was significant (adefovir: -3.50, placebo: -0.67, 95%

confidence interval (CI) for the treatment difference: -3.35, -2.54). The obvious treatment difference was also observed in the three age groups individually.

2. Overall, the percentage of patients with HBV < 1000 copies/mL at Week 48 in the adefovir group was greater than that in the placebo group (adefovir: 21%, placebo: 2%, p-value based on the Fisher's exact test < 0.001). However, there was no significant treatment difference in the 2–6–year or 7–11–year age group, but the proportion appeared to be different between the two treatment groups in the 12–17–year age group.

3. Overall, the mean change in ALT level from baseline to Week 48 was significantly larger than that in the placebo group (adefovir: -58.0 U/L, placebo: -13.6 U/L, 95% CI for the treatment difference: -69.7, -20.8). The treatment difference was not significant in the 2–6–year group, but was obvious in either 7–11–year or 12–17–year age group.

4. Overall, the proportion of subjects with normal ALT at Week 48 among those who had abnormal ALT at baseline was greater in the adefovir group than that in the placebo group (adefovir: 56%, placebo: 21%, p-value based on the Fisher's exact test < 0.001). The treatment difference was not significant in the 2–6–year group, but was obvious in either 7–11–year or 12–17–year age group.

5. At baseline, no subject had undergone HBeAg seroconversion or HBeAg loss. Overall, no treatment difference in the proportion of subjects with HBeAg seroconversion at Week 48 was observed between the two groups. Nor was the treatment difference in the proportion of subjects with HBeAg loss at Week 48. In none of the three age groups were the treatment differences in these two endpoints.

Table 4 in next page displays the sponsor's analysis results for the key secondary efficacy endpoints in detail.

Table 4: Sponsor's Results for Key Secondary Efficacy Endpoints at Week 48

	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)**
Change from baseline in HBV DNA(log10 copies/mL)								
n	21	12	36	18	51	27	108	57
mean (SD)	-3.19 (1.71)	-0.93 (1.23)	-3.38 (1.68)	-0.51 (0.95)	-3.72 (1.45)	-0.66 (1.04)	-3.50 (1.58)	-0.67 (1.05)
treatment difference[1] (95% CI)	-2.26 (-3.46, -1.40)		-2.87 (-3.65, -2.24)		-3.06 (-3.67, -2.53)		-2.83 (-3.35, -2.54)	
Proportion of subjects with HBV DNA < 1000 copies/mL								
n (%)	4 (17%)	1 (8%)	7 (19%)	0 (0%)	13 (23%)	0 (0%)	24 (21%)	1 (2%)
p-value based on Fisher's exact test	0.64		0.082		0.007		<0.001	
Change from baseline in ALT (U/L)								
n	21	12	36	17	51	26	108	55
mean (SD)	-22.2 (99.5)	-12.3 (67.9)	-52.5 (81.9)	1.9 (55.1)	-76.6 (102.3)	-24.5 (63.0)	-58.0 (96.7)	-13.6 (61.7)
treatment difference[1] (95% CI)	-9.9 (-65.5, 46.7)		-54.4 (-94.1, -17.4)		-52.1 (-90.1, -13.0)		-44.4 (-69.7, -20.8)	
Proportion of subjects with normal ALT								
n (%)	7 (30%)	3 (25%)	21 (58%)	3 (16%)	36 (64%)	6 (22%)	64 (56%)	12 (21%)
p-value based on Fisher's exact test	1.00		0.004		< 0.001		< 0.001	
Proportion of subjects with HBeAg seroconversion								
n (%)	5 (22%)	0 (0%)	7 (19%)	0 (0%)	6 (11%)	3 (11%)	18 (16%)	3 (5%)
p-value based on Fisher's exact test	0.15		0.082		1.00		0.051	
Proportion of subjects with HBeAg loss								
n (%)	5 (22%)	7 (19%)	6 (17%)	0 (0%)	7 (13%)	3 (11%)	19 (17%)	3 (5%)
p-value based on Fisher's exact test	0.15		0.082		1.00		0.051	

Source: Source: Study GS-US-103-0518 Interim Clinical Study Report, Section 7, Tables 7-2, 7-3m 7-5, 7-6, 7-8 and 7-9.
[1]treatment difference = mean change in adefovir group – mean change in placebo group.

3.1.5 Reviewer's Comments

The sponsor's analysis considered the ALT as abnormal when it equaled to the upper normal limit (UNL). According to the medical reviewer, Dr. Belew, the ALT should be regarded as normal when it equals to UNL based on Johns Hopkins Harriet Lane Handbook (16th edition). The different definitions of normal ALT led to slightly different results for some ALT-related endpoints such as the primary efficacy endpoint and the secondary efficacy endpoint of the proportion of subjects with normal ALT. Another discrepancy between the sponsor and the reviewer was HBeAg at Week 48 for three subjects: Subjects 1398-1209 and 1400-3125 had negative HBeAg at Weeks 44 and 48, but the sponsor analysis regarded these two subjects had missing HBeAg at Week 48. Subject 1114-3226 had negative HBeAg at Week 44 but missing at Week 48. The statistical reviewer carried Week 44 HBeAg forwards to Week 48 and considered the subject had loss of HBeAG at Week 48, but the sponsor regarded this subject did not achieve HBeAg loss. However, the slight different results between the sponsor and the reviewer as mentioned above did not change the overall conclusion. Table 5 below displays the reviewer's results for primary efficacy endpoint and the proportions of subjects with normal ALT, with HBeAg loss, and with HBe seroconversion at Week 48.

Table 5: Reviewer's Results for Primary Efficacy Endpoint and Some Secondary Efficacy Endpoints (All Treated)

	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)**
Primary efficacy endpoint: proportion of subjects with HBV DNA < 1000 copies/mL and normal ALT at Week 48								
n (%)	4 (17%)	1 (8%)	6 (17%)	0 (0%)	13 (23%)	0 (0%)	23 (20%)	1 (2%)
p-value[1]	0.640		0.083		0.007		<0.001	
Secondary efficacy endpoint: proportion of subjects with normal ALT at Week 48								
n (%)	9 (39%)	3 (25%)	22 (61%)	3 (16%)	38 (68%)	6 (22%)	69 (60%)	12 (21%)
p-value[1]	0.477		0.002		0.001		< 0.001	
Secondary efficacy endpoint: proportion of subjects with HBeAg seroconversion at Week 48								
n (%)	5 (22%)	1 (8%)	7 (19%)	0 (0%)	7 (13%)	4 (15%)	19 (17%)	5 (9%)
p-value[1]	0.640		0.082		0.742		0.172	
Secondary efficacy endpoint: proportion of subjects with HBeAg loss at Week 48								
n (%)	5 (22%)	1 (8%)	7 (19%)	0 (0%)	8 (14%)	4 (15%)	20 (17%)	5 (9%)
p-value[1]	0.640		0.082		1.000		0.169	

[1]The p-value was based on Fisher's exact test.

Furthermore, upon consultant with the medical reviewer, Dr. Belew, adefovir is expected to have an effect directly on HBV and should work similarly regardless of age since it is not an immune modulator. The baseline ALT instead of the age could play a more significant role on determining whether the subject is likely to respond to the treatment. Per Dr. Belew, in practice, whether ALT level is greater than 2xUNL is often used to decide whether a subject should receive a treatment. Therefore, the statistical reviewer conducted an analysis in the subgroup of subjects with baseline ALT > 2xUNL. Overall, the adefovir group had significantly greater percentage of patients having HBV DNA < 1000 copies/mL and normal ALT at Week 48 than the placebo group (adefovir: 21%, placebo: 0%; p-value based on Fisher's exact test = 0.005). In each individual age group, more adefovir-treated subjects than the placebo-treated subjects achieved the primary endpoint, but none of the treatment difference was significant. Table 6 below shows the details of the results.

Table 6: Reviewer's Results for Primary Efficacy Endpoint in Patients with Baseline ALT > 2 x UNL

	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	

Additionally, the subjects in both 2–6–year and 7–11–year groups received the investigational suspension formulation, and the subjects in the 12–17–year group received the tablet formulation. The statistical reviewer performed the analysis to evaluate the treatment effect in each of the two formulations. The group using tablet formulation was essentially the same as the 12–17–year group, and the treatment difference was significant. In the group using the investigational suspension formulation, 17% of adefovir-treated subjects achieved the primary efficacy endpoint compared with 3% of placebo-treated subjects, and the treatment difference was not significant. Table 7 below summarizes the analysis results.

Table 7: Reviewer's Results for Primary Efficacy Endpoint by Different Formulations

	Investigational Suspension Formulation		**Tablet Formulation**	
	Adefovir (n=59)	**Placebo (n=31)**	**Adefovir (n=56)**	**Placebo (n=27)**
n (%)	10 (17%)	1 (3%)	13 (23%)	0 (0%)
p-value based on Fisher's exact test	0.089		0.007	

3.2 Evaluation of Safety

Please refer the medical reviewer, Dr. Belew's review report for the evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Both the sponsor and the reviewer performed the subgroup analysis for the primary efficacy endpoint by gender, race, HBV genotype, prior CHB treatment history and baseline ALT. The reviewer also performed the subgroup analysis by region. There was no apparent treatment by subgroup interaction except for gender. The p-value based on the Breslow-Day test for the homogeneity of the odds ratios for the two gender groups was 0.034. Overall, among the female subjects, there was no obvious treatment difference in spite that more adefovir-treated subjects achieved the primary endpoint compared with placebo-treated subjects (adefovir: 10%, placebo: 5%); but the treatment difference was apparent among the male subjects (adefovir: 26%, placebo 0%). Tables 8 – 13 below display the reviewer's results for the subgroup analyses. Of note, the results by the three age groups are also presented.

Table 8: Reviewer's Subgroup Analysis for Primary Efficacy Endpoint by Race (All Treated)

	2-6 years		7-11 years		12-17 years		total	
Race	**Adefovir (n=23)**	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
White	2/6 (33%)	1/3 (30%)	4/23 (17%)	0/17 (0%)	10/41 (24%)	0/21 (0%)	16/70 (23%)	1/41 (2%)
Black	1/7 (14%)	0/1 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/11 (9%)	0/3 (0%)
Asian	1/8 (13%)	0/6 (0%)	1/8 (13%)	0/1 (0%)	3/13 (23%)	0/5 (0%)	5/29 (17%)	0/12 (0%)
Other	0/2 (0%)	0/2 (0%)	1/2 (50%)	0/0	0/1 (0%)	0/0	1/5 (20%)	0/2 (0%)

Table 9: Reviewer's Subgroup Analysis for Primary Efficacy Endpoint by Gender (All Treated)

	2-6 years		7-11 years		12-17 years		total	
Gender	**Adefovir (n=23)**	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
Female	1/14 (7%)	1/8 (13%)	2/13 (15%)	0/4 (0%)	1/14 (7%)	0/7 (0%)	4/41 (10%)	1/19 (5%)
Male	3/9 (33%)	0/4 (0%)	4/23 (17%)	0/15 (0%)	12/42 (29%)	0/20 (0%)	19/74 (26%)	0/39 (0%)

Table 10: Reviewer's Subgroup Analysis for Primary Efficacy Endpoint by Region (All Treated)

	2-6 years		7-11 years		12-17 years		total	
Region	**Adefovir (n=23)**	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
US	1/13 (8%)	0/4 (0%)	2/9 (22%)	0/4 (0%)	2/13 (15%)	0/5 (0%)	5/35 (14%)	0/13 (0%)
Europe	3/10 (30%)	1/8 (13%)	4/27 (15%)	0/15 (0%)	11/43 (26%)	0/22 (0%)	18/80 (23%)	1/45 (2%)

Table 11: Reviewer's Subgroup Analysis for Primary Efficacy Endpoint by HBV Genotype (All Treated)

	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
Not done	0/0	0/1 (0%)	0/1 (0%)	0/0	0/0	0/0	0/1 (0%)	0/1 (0%)

Table 12: Reviewer's Subgroup Analysis for Primary Efficacy Endpoint by Prior Treatment for CHB (All Treated)

	2-6 years		7-11 years		12-17 years		total	
Prior treatment for CHB	**Adefovir (n=23)**	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
Yes	0/2 (0%)	0/2 (0%)	4/24 (17%)	0/13 (0%)	9/38 (24%)	0/18 (0%)	13/64 (20%)	0/33 (0%)
No	4/21 (19%)	1/10 (10%)	2/12 (17%)	0/6 (0%)	4/18 (22%)	0/9 (0%)	10/51 (20%)	1/25 (4%)

Table 13: Reviewer's Subgroup Analysis for Primary Efficacy Endpoint by Baseline ALT (All Treated)

	2-6 years		7-11 years		12-17 years		total	
Baseline ALT	**Adefovir (n=23)**	**Placebo (n=12)**	**Adefovir (n=36)**	**Placebo (n=19)**	**Adefovir (n=56)**	**Placebo (n=27)**	**Adefovir (n=115)**	**Placebo (n=58)**
≤ 2xULN	1/10 (10%)	1/5 (20%)	1/14 (7%)	0/10 (0%)	6/21 (29%)	0/12 (0%)	8/45 (18%)	1/27 (4%)
>2xULN	3/13 (23%)	0/7 (0%)	5/22 (23%)	0/9 (0%)	7/35 (20%)	0/15 (0%)	15/70 (21%)	0/31 (0%)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Upon the submitted data, the reviewer found that the sponsor did not regard ALT as normal when it equaled to 1 x upper normal limit (UNL), which was different from what is recommended in Johns Hopkins Harriet Lane Handbook (16^{th} edition). Nevertheless, the different definition of normal ALT led to slightly different results for the primary efficacy endpoint and some ALT-related secondary efficacy endpoints, and did not affect the overall conclusion.

Furthermore, upon consultant with the medical reviewer, Dr. Belew, adefovir is expected to have an effect directly on HBV and should work similarly regardless of age since it is not an immune modulator. The baseline ALT level instead of the age could play a more significant role on determining whether the subject is likely to respond to the treatment. The reviewer conducted an analysis in the subgroup of subjects with baseline ALT > 2xUNL, the criteria frequently used in practice to determine whether the subjects should receive a treatment. The analysis results revealed that overall the adefovir group had significantly greater percentage of patients having HBV DNA < 1000 copies/mL and normal ALT at Week 48 than the placebo group (adefovir: 21%, placebo: 0%; p-value based on Fisher's exact test = 0.005). The reviewer further performed the subgroup analysis with respect to the age among these subjects with baseline ALT > 2xUNL, and found that more adefovir-treated subjects than the placebo-treated subjects achieved the primary endpoint in each individual age group, but the treatment difference was insignificant in all three age groups.

Also, since the subjects in both 2–6–year and 7–11–year groups received the investigational suspension formulation and the subjects in the 12–17–year group received the tablet formulation, the reviewer performed the analysis to evaluate the treatment effect in each of the two formulations as measured by the primary efficacy endpoint. The group using tablet formulation was essentially the same as the 12–17–year group, and the treatment difference was significant (adefovir: 23%, placebo: 0%, p-value based on Fisher's exact test = 0.007). In the group using the investigational suspension formulation, 17% of adefovir-treated subjects achieved the primary efficacy endpoint compared with 3% of placebo-treated subjects, and the treatment difference was not significant.

Finally, the subgroup analysis with respect to gender revealed that the treatment effect was different between female and male subjects. The p-value based on the Breslow-Day test for the homogeneity of the odds ratios for the two gender groups was 0.034. Overall, among the female subjects, there

was no obvious treatment difference in spite that more adefovir-treated subjects achieved the primary endpoint compared with placebo-treated subjects (adefovir: 10%, placebo: 5%); but the treatment difference was apparent among the male subjects (adefovir: 26%, placebo 0%).

5.2 Conclusions and Recommendations

After reviewing the 48-week efficacy results for the phase III trial, the statistical reviewer concluded that overall adefovir dipivoxil provided statistical evidence of superior efficacy to the placebo with respect to the primary efficacy endpoint: the proportion of subjects with HBV DNA < 1000 copies/mL and normal ALT at Week 48. Furthermore, the superior efficacy of adefovir was shown in the 12–17–year age group, but not in the 2–6–year or 7–11–year age group.

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