



48-WEEK INTERIM CLINICAL STUDY REPORT

Study Title: A Phase 3 Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (Age 2 to < 18) with Chronic Hepatitis B

Name of Test Drug: Adefovir Dipivoxil

Indication: Chronic Hepatitis B

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study No.: GS-US-103-0518

Phase of Development: Phase 3

IND No.: 52,182
EudraCT No.: 2004-001346-33

Study Start Date: 17 May 2004 (First Subject Screened)
Data Cut-off Date: 04 May 2006 (Last Subject Observation for this Report)

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Report Date: 24 February 2007

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404 USA

Title of Study: A Phase 3 Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (Age 2 to < 18) with Chronic Hepatitis B
Investigators: Multicenter
Study Centers: 26 study centers: United States (12 centers), Poland (5), Germany (4), United Kingdom (3), Belgium (1), and Spain (1)
Publications: None
Study Period: 17 May 2004 (First subject screened) 04 May 2006 (Last subject observation for this report)
Phase of Development: Phase 3
Objectives: The primary objective of this study is as follows: <ul style="list-style-type: none">• To investigate the efficacy of adefovir dipivoxil for the treatment of chronic hepatitis B (CHB) in children and adolescents (age 2 to < 18) compared to placebo following 48 weeks of treatment The secondary objectives of this study are as follows: <ul style="list-style-type: none">• To investigate the safety of adefovir dipivoxil for the treatment of CHB in children and adolescents (age 2 to < 18) compared to placebo following 48 weeks of treatment• To evaluate the proportion of children and adolescents who experience HBeAg and HBsAg seroconversion following 48 weeks of treatment with adefovir dipivoxil or placebo• To evaluate the development of conserved site mutations associated with resistance to adefovir dipivoxil• To evaluate the safety (including assessment of growth and renal function) and efficacy of adefovir dipivoxil in children and adolescents for up to 5 years

STUDY SYNOPSIS (CONTINUED)

Methodology: There are two study periods:

Weeks 1–48: The first 48 weeks of the study were a randomized, double-blind, placebo-controlled, parallel-group treatment period. Randomization was stratified on 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). This study period has been completed, and its findings are presented in this report.

Weeks 49–240: At Week 48, all placebo-treated subjects who did not exhibit HBeAg or HBsAg seroconversion at Week 44, plus all adefovir-dipivoxil-treated subjects, were offered the opportunity to receive open-label adefovir dipivoxil for up to an additional 192 weeks. This study period is ongoing.

Number of Subjects (Planned and Analyzed):

Planned: ≥ 150 subjects

Analyzed: 173 subjects

Diagnosis and Main Criteria for Inclusion: The study enrolled treatment-naive and treatment-experienced pediatric subjects (2 to < 18 years old at the first dose of study treatment) who had HBeAg+ CHB, serum hepatitis B virus (HBV) DNA ≥ 10⁵ copies/mL, compensated liver disease, and calculated creatinine clearance ≥ 80 mL/min.

Subjects who had previously participated in Gilead pharmacokinetics Study GS-02-517 were allowed to enroll regardless of screening serum HBV DNA or ALT concentration if they met all other entry criteria.

Duration of Treatment: The results of the first 48 weeks of treatment with adefovir dipivoxil or placebo are presented in this report.

Test and Reference Products, Doses, Mode of Administration, and Batch No.:

Test and Reference Products and Doses:

- Subjects 2 to < 7 years: investigational oral suspension of adefovir dipivoxil, 0.3 mg/kg once daily (or matching placebo)
- Subjects ≥ 7 to < 12 years: investigational oral suspension of adefovir dipivoxil, 0.25 mg/kg once daily (or matching placebo)
- Subjects ≥ 12 to < 18 years: adefovir dipivoxil tablet (marketed formulation), 10 mg once daily (or matching placebo)

The adefovir dipivoxil dose was not to exceed 10 mg/day. Subjects who had their 12th birthday during the 48-week double-blind treatment period continued on the oral suspension formulation (at a dose of 10 mg/day) until the end of Week 48.

STUDY SYNOPSIS (CONTINUED)

Test and Reference Products, Doses, Mode of Administration, and Batch No. (Continued):

Mode of Administration: Oral

Lot Numbers:

- Adefovir dipivoxil oral suspension (investigational formulation): U302A1, U401A1
- Adefovir dipivoxil tablet (marketed formulation): D301A1, D403A1
- Placebo oral suspension: U304A1
- Placebo tablet: D008A1, D102A1

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

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

Secondary Efficacy Endpoints:

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

STUDY SYNOPSIS (CONTINUED)

Criteria for Evaluation (Continued):

Efficacy (Continued):

Secondary Efficacy Endpoints (Continued):

- The proportion of subjects with HBs antigen loss (defined as having negative serum HBsAg for subjects with positive serum HBsAg at baseline) by study visit

The LLQ of the HBV DNA assay was 29 IU/mL (equivalent to 169 copies/mL).

Secondary endpoints were evaluated comparing the treatment effect in the CHB–treatment-experienced subject strata to the treatment effect in the treatment-naive subject strata.

Pharmacokinetics: A plasma sample for pharmacokinetic analysis was obtained from each subject at the study visits at baseline and Weeks 4, 8, 12, 24, 36, 44, and 48, as well as any early termination visit before Week 48; samples were obtained at random times relative to the most recent dose of study treatment. Plasma adefovir concentrations were measured, and the following adefovir pharmacokinetic parameters were estimated for each age group based on pooled plasma concentrations of adefovir: maximum plasma concentration of drug (C_{max}), area under the concentration versus time curve over the dosing interval (AUC_{0-24}), time to maximum plasma concentration (T_{max}), and terminal elimination half-life ($T_{1/2}$).

Safety: Adverse events (AEs); clinical laboratory tests, including tests of hepatic and renal function; vital signs; and physical examinations (including monitoring for possible effects on growth)

Statistical Methods:

The analysis included data through 48 weeks of treatment. The efficacy and safety analyses used the Randomized-and-Treated analysis set, which included all subjects who were randomized and received at least one dose of study medication. The pharmacokinetics analysis used the Pharmacokinetics analysis set, which included all subjects who had at least one plasma adefovir concentration measurement (i.e., all subjects in the adefovir dipivoxil group).

The age groups used in the analysis and presentation of data are based on age at the first dose of study treatment.

Efficacy: In the Statistical Analysis Plan (which was finalized before unblinding the study), the planned analysis of the primary efficacy endpoint was a comparison of the treatment groups using 95% confidence intervals (CIs) of the difference between the groups (as well as comparison between groups with data stratified by age group and by previous treatment for hepatitis B). However, after unblinding the results, due to the small number of responders in the placebo group, it was determined that a statistical exact test would be more appropriate in the evaluation of treatment group differences. Therefore, for the analysis of the primary endpoint, the results were analyzed by study visit, and a Fisher's Exact test was used to evaluate treatment differences between the adefovir dipivoxil and placebo groups.

STUDY SYNOPSIS (CONTINUED)

Statistical Methods (Continued):

Efficacy (Continued): Also in the Statistical Analysis Plan, it was planned that the differences between the treatment groups for each of the secondary endpoints would be analyzed using 95% CIs of the difference between the groups (using means for continuous endpoints and percentages for categorical endpoints). However, after unblinding the results, due to the small number of responders in the placebo group, it was determined that a statistical exact test would be more appropriate in the evaluation of treatment group differences. Therefore, for the analysis of the categorical secondary endpoints, the results were analyzed by study visit and a Fisher's Exact test was used to evaluate treatment differences between the adefovir dipivoxil and placebo groups. For continuous secondary endpoints, the 95% CIs were used because they are still appropriate for evaluation of treatment group differences.

Pharmacokinetics: Mean and median adefovir plasma concentration-time profiles were constructed with pooled adefovir plasma concentrations by age group. Pharmacokinetic parameters were estimated by application of a nonlinear curve-fitting software WinNonlin[®] (Professional Edition, Version 5.0.1; Pharsight Corporation, Mountain View, CA) using both noncompartmental method and compartment model.

Safety: AEs were mapped using the Medical Dictionary for Regulatory Activities (MedDRA), Version 9.0. AEs were summarized by age group and treatment. For each preferred term that occurred in at least 10% of subjects overall, a Fisher's exact test was used to compare the treatment groups.

For a subset of laboratory safety parameters, summary statistics were calculated, and the maximum postbaseline graded laboratory abnormalities were summarized.

SUMMARY – RESULTS:

For simplicity, in the remainder of this synopsis, subjects age 2 to < 7 years are referred to as age 2–6 years, those age ≥ 7 to < 12 years are referred to as age 7–11 years, and those age ≥ 12 to < 18 years are referred to as age 12–17 years. These age groups are based on the subject's age at the first dose of study treatment.

Efficacy Results: In the 12–17-year age group, significantly more adefovir-dipivoxil–treated subjects achieved the primary efficacy endpoint—serum HBV DNA < 1000 copies/mL and normal ALT at the end of blinded treatment—compared with placebo-treated subjects (23% vs 0, $p = 0.007$). In the younger age groups (2–6, 7–11, and pooled 2–11 years), the differences between adefovir dipivoxil and placebo at the end of blinded treatment were not statistically significant, although three adefovir-dipivoxil–treated subjects (13%) in the 2–6-year age group and six adefovir-dipivoxil–treated subjects (17%) in the 7–11-year age group achieved the primary efficacy endpoint. Pooling data across all age groups, significantly

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS (Continued):

Efficacy Results (Continued): more adefovir-dipivoxil–treated subjects had serum HBV DNA < 1000 copies/mL and normal ALT at the end of blinded treatment compared with placebo-treated subjects (19% vs 2%, $p < 0.001$).

Decreased efficacy in the two younger age groups was also seen for a number of the secondary efficacy endpoints. For the percentage of subjects with serum HBV DNA < 1000 copies/mL at the end of blinded treatment, there was a statistically significant difference between the adefovir-dipivoxil– and placebo-treated subjects in the 12–17-year age group (23% adefovir dipivoxil vs 0 placebo, $p = 0.007$). However, in the younger age groups, the differences between adefovir-dipivoxil– and placebo-treated subjects were not statistically significant (2–6 years: 17% adefovir dipivoxil vs 8% placebo; 7–11 years: 19% vs 0; pooled 2–11 years: 19% vs 3% [$p = 0.052$ for pooled 2–11-year subjects]). Pooling data across all age groups, significantly more adefovir-dipivoxil–treated subjects had a serum HBV DNA concentration < 1000 copies/mL at the end of blinded treatment compared with placebo-treated subjects (21% vs 2%, $p < 0.001$).

In the categorical analysis of serum HBV DNA concentrations at the end of double-blind treatment (i.e., < 169 copies/mL; ≥ 169 but < 1000 copies/mL; ≥ 1000 but < 10^4 copies/mL; $\geq 10^4$ but < 10^5 copies/mL; $\geq 10^5$ but < 10^6 copies/mL; $\geq 10^6$ copies/mL), among adefovir-dipivoxil–treated subjects, older subjects were more likely than younger subjects to have an HBV DNA concentration < 1000 copies/mL, while younger subjects were more likely to have a concentration $\geq 10^6$ copies/mL. At the end of blinded adefovir dipivoxil treatment, the HBV DNA concentration was < 1000 copies/mL in 17% of subjects in the 2–6-year age group, 19% of subjects in the 7–11-year age group, and 23% of subjects in the 12–17-year age group (and 19% in the pooled 2–11-year groups). HBV DNA was $\geq 10^6$ copies/mL in 61% of the subjects in the 2–6-year age group, 36% of the subjects in the 7–11-year age group, and 27% of the subjects in the 12–17-year age group (and 46% in the pooled 2–11-year groups).

For the change from baseline in serum HBV DNA, in each of the three age groups there was a statistically significant difference between the adefovir-dipivoxil– and placebo-treated subjects in the change from baseline to Week 48 (statistical assessments based on the 95% CIs of the treatment differences in the change from baseline). However, for adefovir-dipivoxil–treated subjects, the magnitude of the change decreased somewhat as the age of the subjects decreased: In the 12–17-year age group, the median change from baseline was $-3.46 \log_{10}$ copies/mL (mean, -3.72); in the 7–11-year age group, it was -3.27 copies/mL (mean, -3.38); and in 2–6-year age group, it was -2.78 copies/mL (mean, -3.19). When change-from-baseline data were pooled for analysis, the statistically significant difference between the adefovir-dipivoxil– and placebo-treated subjects in the change from baseline to Week 48 was still evident; this was true when data were pooled across all age groups, and when data from the 2–11-year age groups were pooled.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS (Continued):

Efficacy Results (Continued): For the percentage of subjects with normal serum ALT at the end of blinded treatment, there were statistically significant differences between adefovir dipivoxil and placebo in the 12–17-year age group (64% adefovir dipivoxil vs 22% placebo, $p < 0.001$) and the 7–11-year age group (58% vs 16%, $p = 0.004$), but not in the 2–6-year age group (30% vs 25%). When data from the 2–6- and 7–11-year age groups were pooled for analysis, the difference between adefovir dipivoxil and placebo was statistically significant (48% adefovir dipivoxil vs 19% placebo, $p = 0.012$). Pooling data across all age groups, significantly more adefovir-dipivoxil–treated subjects had normal ALT at the end of blinded treatment compared with placebo-treated subjects (56% vs 21%, $p < 0.001$).

For the change from baseline in serum ALT, there was a statistically significant difference between the adefovir-dipivoxil– and placebo-treated subjects in the change from baseline to Week 48 in the 12–17- and 7–11-year age groups, but not in the 2–6-year age group (statistical assessments based on the 95% CIs of the treatment differences in the change from baseline). When change-from-baseline data were pooled for analysis, there was a statistically significant difference between the adefovir-dipivoxil and placebo groups in the change from baseline to Week 48; this was true when data were pooled across all age groups, and when data from the 2–11-year age groups were pooled.

For the percentage of subjects with HBeAg seroconversion plus serum HBV DNA < 1000 copies/mL plus normal ALT at the end of blinded treatment, there were no statistically significant differences between adefovir-dipivoxil–treated and placebo-treated subjects in any of the three age groups. However, when the data were pooled for analysis, the difference between the treatment groups was statistically significant, both when data were pooled for subjects in the 2–11 year groups (14% adefovir dipivoxil vs 0 placebo, $p = 0.048$) and when data from all three age groups were pooled (11% adefovir dipivoxil vs 0 placebo, $p = 0.009$).

For the percentage of subjects with HBeAg seroconversion at the end of blinded treatment, there were no statistically significant differences between adefovir-dipivoxil–treated and placebo-treated subjects in any of the three age groups. However, when the data from the 2–6- and 7–11-year groups were pooled for analysis, the difference between the treatment groups was statistically significant (20% adefovir dipivoxil vs 0 placebo, $p = 0.007$). When data were pooled across all three age groups, the difference between the treatments was not statistically significant (16% adefovir dipivoxil vs 5% placebo, $p = 0.051$). Findings for loss of HBeAg at the end of blinded treatment were very similar to those for HBeAg seroconversion.

One adefovir-dipivoxil–treated subject experienced HBsAg seroconversion.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS (Continued):

Efficacy Results (Continued): No subject developed the rtA181V or rtN236T mutation associated with ADV resistance by Week 48. The rtA181T mutation was identified in three lamivudine-experienced adefovir-dipivoxil-treated subjects at baseline and Week 48; the effects of adefovir dipivoxil on serum HBV DNA and ALT in these three subjects did not appear to differ markedly from the effects observed in other subjects.

Pharmacokinetic Results: Adefovir plasma exposure was comparable among the three age groups. Of importance, all three age groups of pediatric subjects achieved the target range of adefovir plasma exposure (C_{max} and AUC_{0-24}) that had been identified in adult CHB patients with established safety and efficacy profiles (Gilead Study GS-00-472). In GS-00-472, the median C_{max} in adult CHB patients was 16.7 ng/mL (range, 9.2–38.7) and the steady-state AUC_{0-24} was 185.6 ng•h/mL (range, 124.3–367.0). In the current study, based on the one-compartment model and median concentration data, the predicted C_{max} values of the age groups in the current study ranged from 16.01 to 22.26 ng/mL, and the predicted AUC_{0-24} values ranged from 201.24 to 239.77 ng•h/mL.

Safety Results: Adefovir dipivoxil treatment was well tolerated in all age groups in this first large study in pediatric subjects with CHB. The events observed in pediatric subjects were a subset of those previously seen in adults; no new AEs were identified in pediatric subjects. Furthermore, no age-related patterns of clinical concern were evident.

The same percentage of subjects in the adefovir dipivoxil and placebo groups reported AEs (83%), most of which were mild or moderate (Grade 1 or 2) and were judged by the investigator to be unrelated to treatment. The most common AEs in both treatment groups were typical childhood illnesses and their signs and symptoms. There were no AEs suggestive of adverse effects on renal function, and no remarkable findings in parameters related to renal function. No subject experienced hepatic decompensation. Treatment-related AEs were reported for 14% of adefovir-dipivoxil-treated and 10% of placebo-treated subjects. No treatment-related event led to permanent discontinuation of treatment.

No study subject died. A total of 6% of adefovir-dipivoxil-treated and 9% of placebo-treated subjects had at least one SAE. The only treatment-related SAE in an adefovir dipivoxil subject was a Grade-3 treatment-related SAE of increased hepatic enzymes that resolved during continuing study treatment. One subject permanently discontinued treatment because of an event: an SAE of Grade-2 worsening of a pre-existing behavioral disorder that was judged unrelated to study treatment. Only one SAE occurred in more than a single subject: unrelated Grade-2 pyrexia in two adefovir-dipivoxil-treated subjects.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS (Continued):

Safety Results (Continued): Grade-3 or 4 AEs were reported for two adefovir-dipivoxil-treated subjects (2%) and six placebo-treated subjects (10%) during the double-blind treatment period. The events in adefovir-dipivoxil-treated subjects were the Grade-3 treatment-related SAE of increased hepatic enzymes discussed in the paragraph above, and Grade-3 AEs of toothache and bronchitis judged unrelated to treatment.

The small numbers of serious or severe AEs make it difficult to assess those data for age-related trends in the age/treatment subgroups.

Most graded abnormalities in laboratory parameters were mild or moderate, and there were no patterns of change in the adefovir dipivoxil group that were of clinical concern.

Treatment-emergent graded abnormalities in serum creatinine occurred in 16% (18/115) of the adefovir-dipivoxil-treated subjects and 10% (6/58) of the placebo-treated subjects. All of the serum creatinine abnormalities were mild (Grade 1). Three adefovir-dipivoxil-treated subjects had increases in ALT that met the protocol's definition of a severe hepatic flare. All three events resolved without intervention during ongoing adefovir dipivoxil treatment.

CONCLUSIONS:

The findings of 48 weeks of double-blind adefovir dipivoxil treatment in pediatric subjects with HBeAg+ CHB lead to the following conclusions:

- Over all subjects, adefovir dipivoxil demonstrated a statistically significant difference from placebo in the proportion of subjects achieving the primary efficacy endpoint (i.e., HBV DNA < 1000 copies/mL plus normal ALT at the end of blinded treatment), the proportion with HBV DNA < 1000 copies/mL at the end of blinded treatment, and the proportion with normal ALT at the end of blinded treatment. However, these statistical differences and the magnitude of the observed efficacy responses were not robust across all age groups.
- Adefovir dipivoxil showed significant antiviral efficacy in subjects in the 12–17-year age group, similar to that seen in adults with HBeAg+ CHB. There were statistically significant differences between the adefovir dipivoxil and placebo groups in the proportion of subjects achieving the primary efficacy endpoint (HBV DNA < 1000 copies/mL plus normal ALT at the end of blinded treatment), the proportion with HBV DNA < 1000 copies/mL at the end of blinded treatment, and the change from baseline to Week 48 in HBV DNA and ALT. The same proportion of adefovir-dipivoxil- and placebo-treated subjects had HBeAg seroconversion at the end of blinded treatment.

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS (Continued):

- Adefovir dipivoxil appears to be less effective in subjects 2–11 years old than in adolescents and adults. In these 2–11-year-old subjects, there was a lower proportion of adefovir-dipivoxil–treated subjects achieving the primary efficacy endpoint (HBV DNA < 1000 copies/mL and normal ALT at the end of blinded treatment) that was not statistically different from the response observed in the placebo group.
- In the two younger age groups, the proportions of subjects with very high viral loads (i.e., HBV DNA $\geq 10^6$ copies/mL) at the end of blinded treatment were high (61% in the 2–6-year group, 36% in the 7–11-year group). Based on findings in adult patients, persistent viremia after 48 weeks of treatment may put patients at an increased risk for subsequent development of adefovir resistance.
- Adefovir plasma concentrations were comparable in the three pediatric age groups, and each age group achieved adefovir concentrations in the target range—a range that was based on adefovir plasma concentrations in adult CHB patients with established safety and efficacy profiles.
- By Week 48, no subject developed the rtA181V or rtN236T mutation associated with adefovir resistance. The rtA181T mutation was identified in three lamivudine-experienced adefovir-dipivoxil–treated subjects at baseline and Week 48; the effects of adefovir dipivoxil on serum HBV DNA and ALT in these three subjects did not appear to differ markedly from the effects observed in other subjects.
- Adefovir dipivoxil was well tolerated across the pediatric age groups. No new AEs were identified: The events observed in pediatric subjects were a subset of those previously seen in adults. There were no discontinuations for treatment-related AEs, and no remarkable findings in parameters related to renal function. The most common AEs were typical childhood illnesses and their signs and symptoms, and they were similar in the adefovir dipivoxil and placebo groups.
- Most graded abnormalities in laboratory parameters were mild or moderate, and there were no patterns of change in the adefovir dipivoxil group that were of clinical concern.