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APPLICATION NUMBER:

21-003/SE1-002

21-004/SE1-002

MEDICAL REVIEW

Medical Officer's Review
Supplemental New Drug Application
NDAs 21-003 and 21-004 (SE01-002)

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Applicant: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Drug name: Lamivudine (Epivir-HBV, 3TC, GR109714X)

Dosage form: Tablets 100 mg (NDA 21-003)
Solution 5 mg/ml (NDA 21-004)

Route of administration: Oral

Proposed indication: Treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation in patients 2 years of age and older

Related INDs: [redacted]

Related NDAs: NDA 20-564 (lamivudine tablets 150 mg)
NDA 20-596 (lamivudine solution 10 mg/ml)
NDA 20-857 (lamivudine/zidovudine tablets)

Related Documents: Medical Officer Review of the original NDAs 21-003 and 21-004
Biopharmaceutics Review of the original NDAs 21-003 and 21-004
Statistical Review of SE01-002 for NDAs 21-003 and 21-004

Amendments: June 7, 2001; June 13, 2001; June 22, 2001

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I. Resume

Lamivudine, a nucleoside analogue, was approved for the treatment of HIV-infected adults in November 1995, and clinical trial information for HIV-infected children was added in 1999. Lamivudine tablets and oral solution were then approved for the treatment of chronic hepatitis B infection in adults on December 8, 1998. GlaxoSmithKline has submitted an efficacy supplement for the treatment of chronic hepatitis B infection in children two years of age and older. This proposal is supported by one Phase III pediatric clinical trial, a Phase II pharmacokinetic trial,

NUCB2020 was a Phase II, randomized, multicenter study of the pharmacokinetics, safety, and antiviral activity of lamivudine in 53 children from two to 17 years. Children with chronic hepatitis B infection were divided into one of three strata by age: Stratum 1 enrolled children from two to six years of age, Stratum 2 enrolled children from seven to 12 years of age, and Stratum 3 enrolled adolescents from 13 to 17 years of age. Children in Strata 1 and 2 were then randomized to one of four lamivudine doses: 0.35 mg/kg twice daily, 1.5 mg/kg twice daily, 3.0 mg/kg once daily, and 4.0 mg/kg twice daily. Adolescents received the approved adult dose of 100 mg daily. All study subjects were treated for four weeks and observed for an additional 12 weeks. Pharmacokinetic measurements were obtained on day one and day 28. Dose selection for children younger than 13 years was based on dose-response relationships; the median decrease in HBV DNA levels and the proportion of subjects were similar for subjects in the treatment groups receiving 1.5 mg/kg twice daily, 3.0 mg/kg once daily, and 4.0 mg/kg twice daily. Because of the comparable efficacy results for these three dose levels and the ease of once daily administration, the applicant selected 3.0 mg/kg once daily as the appropriate dose for study in pediatrics patients 12 years of age and younger. Dose selection for adolescents was based on pharmacokinetic data only; pharmacokinetic measurements obtained with 100 mg daily in children 13 years of age and older were comparable to those obtained in previous studies of adults. When preliminary four-week antiviral activity data were evaluated, adolescents had a lesser treatment effect than younger children. Lamivudine was well tolerated in NUCB2020, and no safety concerns were raised in this study. Overall, the results of NUCB2020 allowed for the selection of an acceptable dose of lamivudine for the treatment of chronic hepatitis B in children, and provided preliminary information on the antiviral activity and safety of lamivudine in the treatment of chronic hepatitis B infection in children.

NUC30903 was a Phase III, double-blind, placebo controlled, multicenter trial of the safety and efficacy of lamivudine in the treatment of chronic hepatitis B infection in children from two to 17 years of age. Two hundred eighty-eight study subjects were randomized to receive 52 weeks of either lamivudine 3 mg/kg daily (maximum of 100 mg daily) or placebo in a 2:1 ratio. The primary efficacy endpoint in NUC30903 was the proportion of subjects with a complete virologic response (CVR) at week 52; CVR was defined as loss of HBeAg and undetectable HBV DNA levels. A complete virologic response was seen in 23% of lamivudine subjects and 13% of placebo subjects ($p=0.037$).

This statistically significant difference was maintained after analyses of several different treatment populations by the applicant. However, a slightly higher p value was obtained ($p=0.085$) in a sensitivity analysis performed by the Division. This change in statistical significance must be viewed with caution. First, statistically significant results obtained by the applicant were for predefined study analyses. Second, the relationship of CVR to other outcomes such as histopathologic changes and cirrhosis or end-stage liver disease has not been well established. Change in liver histology was used as the primary efficacy endpoint in the clinical trials supporting the approval of Epivir-HBV in adults. While improvement in liver histology was seen in slightly more than one-half of subjects, serologic response such as loss of HBeAg was noted in only 17 to 32% of subjects. Third, subjects in the lamivudine group had a better response for all secondary efficacy endpoints than subjects in the placebo group, so efficacy was supported by additional analyses of data and not just results for the primary efficacy endpoint.

On further analyses of NUC30903, concerns were raised by analyses by baseline HBV disease characteristics and by subgroup analyses. Certain baseline characteristics of HBV disease influenced the treatment effect. A greater proportion of subjects with higher ALT values, higher Knodell scores, and lower HBV DNA levels had a complete virologic response. On subgroup analyses, treatment effect varied by age; younger children had a substantially better treatment effect than adolescents. The reason for this difference was not determined. Treatment differences were also noted in subgroup analyses for gender, ethnic origin, and country. However, these treatment differences were largely due to a varying proportion of placebo subjects achieving a CVR, which may have been due to small numbers of patients in the individual subgroups or to the normal variation of disease typically seen with chronic HBV infection. Although these treatment differences are concerning and they suggest that there are certain subgroups of patients who would benefit more from treatment with lamivudine, it must be remembered that this study was not powered for subgroup analysis.

Because lamivudine is currently approved for the treatment of HIV-infected children three months of age and older at a higher dose than the dose proposed for use in children with chronic hepatitis B infection, the safety profile of lamivudine in children has been well described. No new safety concerns were raised in this efficacy supplement.

Eighteen percent of subjects who received lamivudine in NUC30903 had YMDD variant HBV isolated at week 52. YMDD variants were noted more frequently in subjects who had higher HBV DNA at baseline, younger subjects, and smaller subjects. The reasons for these differences have not been determined. Another concern was the decrease in efficacy noted in subjects with YMDD variant HBV. Although subjects with YMDD variant HBV had ALT and HBV DNA responses that were intermediate between patients with wild type virus who received lamivudine and placebo subjects, there was no difference in response to serologic endpoints for subjects with YMDD-positive HBV and placebo subjects. In addition, there was a negative correlation between YMDD variant virus and all efficacy endpoints.

[redacted]

In conclusion, information submitted in this application supports the treatment of chronic hepatitis B infection in children two to 17 years of age with lamivudine 3 mg/kg daily to a maximum of 100 mg for 52 weeks. The Phase III pediatric clinical trial showed a treatment benefit with lamivudine as measured by the primary and secondary efficacy endpoints defined in the study protocol. Furthermore, no new safety issues were seen in these studies. In addition, lamivudine is currently approved for the treatment of adults with chronic HBV infection; safety and efficacy data concerning the use of lamivudine in clinical trials of adults with chronic hepatitis B infection and in HIV-infected children and adults add additional support for the use of lamivudine in children with chronic hepatitis B infection. Although concerns arose because of differential treatment effects noted for certain subgroups in NUC30903 and NUCB2020, most notably the lesser treatment effect in adolescents, these studies were not powered for subgroup analysis. These issues should be further investigated by the applicant as part of their Phase IV commitments. Concerns about the association of YMDD mutations and decreased efficacy also arose, and the significance of this finding should also be further investigated by the applicant.

II. Regulatory Background

The original IND for lamivudine for the treatment of HIV infection was submitted on June 21, 1991. Lamivudine received accelerated approval for use as part of combination antiretroviral therapy for HIV in November 1995. Clinical trial data for the use of lamivudine in HIV-infected children three months of age and older were added to the package insert in March 1999. Traditional approval was granted on April 11, 1997. Lamivudine tablets and oral solution (10 mg/ml) are currently approved for use with other antiretroviral agents in the treatment of HIV infection in children three months of age and older.

[redacted] was submitted to the FDA on October 23, 1992 to support the study of lamivudine in the treatment of chronic hepatitis B infection. NDA 21-003 (lamivudine 100 mg tablets) and NDA 21-004 (lamivudine 5mg/ml oral solution) were subsequently submitted on June 24, 1998 and June 29, 1998 respectively. Lamivudine was approved for the treatment of chronic hepatitis B infection in adults on December 8, 1998.

The protocol for study NUCB2020, a Phase II study of lamivudine in the treatment of children with chronic hepatitis B infection was submitted to [redacted] on July 14, 1997. Results from the study were reported in NDAs 21-003 and 21-004 but were not considered to be sufficient for approval of the use of lamivudine to treat chronic hepatitis

B infection in children. The protocol for study NUC30903, a Phase III, double-blind, placebo controlled, multicenter study of lamivudine in the treatment of children with chronic hepatitis B infection, was submitted on June 30, 1998. Results from both NUCB2020 and NUC30903 are reported in the current application.

This pediatric efficacy supplement contained nineteen volumes. Additional submissions for this supplement included the Safety Update Report submitted on June 7, 2001 which will be reviewed in an addendum to this review and amendments received on June 7, June 14, and June 22, 2001. Divisional meetings to discuss this supplement were held on April 25; May 18, 23, and 30, and June 6, 11, and 20, 2001. Additional discussions with the Division's pediatric team were held on May 29 and June 5, 2001; conclusions from these meetings supported the approval of this supplement.

III. Clinical Studies of Epivir HBV in Pediatric Patients

A. Study NUCB2020

1. Study Design

Study NUCB2020, "A Phase II, Dose-Ranging Study of the Pharmacokinetics of Lamivudine in Children and Adolescents with Chronic Hepatitis B Virus Infection," was conducted in four study centers in Canada, the United Kingdom and Belgium from June 1997 to January 1998. Since this study was previously reviewed by the Medical Officer and the Biopharmaceutics reviewer in their reviews of the original NDAs 21-003 and 21-004, the study results will only be briefly addressed in this review.

Study NUCB2020 was a randomized, multicenter study of the pharmacokinetics, safety, and antiviral activity of Epivir-HBV in 53 children ranging in age from two to 17 years. This study enrolled children with chronic HBV infection, which was defined using laboratory criteria (HBsAg positive for six months prior to screening, positive HBeAg, and positive HBV DNA by the [redacted] assay). Children with AST or ALT values greater than 300 IU/L, decompensated liver disease, bone marrow suppression, abnormal renal function, pancreatitis, or coinfection with Hepatitis C virus or human immunodeficiency virus were excluded from participation. Enrolled patients were divided by age into one of three strata: Stratum 1 enrolled children from 2 to 6 years of age, Stratum 2 enrolled children from 7 to 12 years, and Stratum 3 enrolled adolescents from 13 to 17 years. Children within Stratum 1 and Stratum 2 were then randomized to receive one of four doses of lamivudine oral solution (see Table 1). All adolescents in Stratum 3 received lamivudine, one 100 mg tablet daily, which is the dose currently approved for the treatment of chronic HBV infection in adults. Patients received lamivudine for four weeks and were then followed for an additional 12 weeks. Pharmacokinetic parameters were measured on day one and on day 28 with additional trough samples collected predosing on day 14 and 24 hours post dosing on day 29 for subjects in the 3 mg/kg/day and 100 mg/kg/day groups. Hepatitis B DNA levels and serologic measurements were collected on screening, on day one prior to dosing, and at

weeks 2, 4, 8, and 16. Safety data were collected from reported adverse events and from chemistry and hematology laboratory measurements obtained at each study visit.

2. Study Population and Patient Accounting

Fifty-three children were enrolled into study NUCB2020. The mean age was 8.9 years, most children (58%) were male, and the majority were Asian in ethnic origin (58%). Most children had acquired hepatitis B infection perinatally (63%) and the average time since diagnosis of HBV infection was 2.7 years.

Enrolled children were divided by age into treatment groups, and patients less than 13 years of age were randomized to receive one of four different dosing regimens of lamivudine oral solution. The treatment groups by age and by lamivudine dosage are shown in Table 1.

Table 1: Treatment Groups (Modified Intent-to-Treat Population) in Study NUCB2020

Age (yrs)	0.35 mg/kg bid	1.5 mg/kg bid	3.0 mg/kg q day	4.0 mg/kg bid	100 mg q day	Total
2 – 6	3	4	5	5	0	17
7 – 12	5	6	6	6	0	23
13 – 17	0	0	0	0	12	12
Total	8	10	11	11	12	---

Source: Study NUCB2020. CSR, Volume 6.1, Table 5.

No patients were withdrawn from the study or were lost to follow-up. One patient was excluded from the intent-to-treat analysis, because he did not have hepatitis B surface antigen documented for six months prior to screening. Three patients had protocol violations: the two year old male who had not been HBsAg positive for six months prior to study screening, a two year old Asian female who was randomized to lamivudine at 0.35 mg/kg/bid but received 1.75 mg/kg/bid, and a seven year old white male with AST and ALT levels greater than 300 IU/L due to Duchenne syndrome. Three dosing errors were made: the two year old mentioned previously was randomized to the 0.35 mg/kg/bid lamivudine dose but received 1.75 mg/kg/bid, a five year old was randomized to 3 mg/kg/day but received lamivudine 1.5 mg/kg/bid, and a two year old was randomized to 0.35 mg/kg/bid but received 3 mg/kg/day. During the modified intent-to-treat analysis, these children were included in the treatment groups to which they were randomized.

3. Pharmacokinetic Analysis

Please see Dr. Rajagopalan's review for the original New Drug Application and Dr. DiGiacinto's review for this supplemental NDA.

Results for all 53 patients were included in the pharmacokinetic analysis. Pharmacokinetic sampling was obtained on days one and 28, and AUC values are shown in Table 2.

When the pharmacokinetic parameters were examined by patient age, higher oral clearance measurements were noted in the younger children. Oral clearance for children from 2 to 6 years of age was 11.87 ml/min/kg, for children 7 to 12 years of age was 9.58 ml/min/kg, and for children 13 to 17 years of age was 7.75 ml/min/kg. These results were consistent with clearance values previously noted in studies of HIV-infected children.

In order to select a dose of lamivudine oral solution for pediatric patients 12 years of age and younger, lamivudine exposure and plasma HBV DNA response were compared for each treatment group. The steady state AUC_{24} for each dose level was compared to the log reduction in HBV DNA levels and to the percentage of patients with undetectable plasma HBV levels on day 28. Results of this comparison are shown in Table 2.

Table 2: Comparison of Plasma HBV DNA Response and Lamivudine Exposure by Treatment Group in Study NUCB2020

	0.35 mg/kg bid	1.5 mg/kg bid	3.0 mg/kg q day	4.0 mg/kg bid
AUC_{24} (ng•h/ml)	1,715	5,231	5,784	15,123
# (%) of Patients with undetectable HBV DNA	2/8 (25%)	4/10 (40%)	5/11 (45%)	7/11 (64%)
Log Reduction in HBV DNA	- 2.6	- 3.1	- 3.0	- 3.1

Source: Study NUCB2020, CSR, Volume 6.1, Tables 12, 19, and 26.

When the proportion of patients with undetectable plasma HBV DNA levels were compared between treatment groups, the responses in the 1.5 mg/kg/bid, 3.0 mg/kg/day, and the 4.0 mg/kg/bid were similar. However, there was a lesser response in the 0.35 mg/kg/bid treatment group, which was also seen in the log reduction of plasma HBV DNA. It can be assumed that patients in the 0.35 mg/kg/bid group had a lesser response due to lower plasma lamivudine concentrations. There was a similar proportion of subjects with undetectable HBV DNA at doses of 1.5 mg/kg/bid, 3.0 mg/kg/day, and 4.0 mg/kg/bid, and all three doses resulted in greater than a 99% reduction in HBV DNA levels at week 4. In addition, trough lamivudine levels for all three doses were greater than the in vitro IC_{50} for hepatitis B virus (5-7 ng/ml). Because the response rates for these three dose levels were similar but the 3.0 mg/kg required only once daily administration, the applicant selected 3.0 mg/kg/day as the lamivudine dose for further study.

Dose selection for adolescents was based solely on the pharmacokinetic results of NUCB2020; adolescent patients in this study had plasma lamivudine concentrations that were consistent with those previously noted in adults with chronic HBV infection. The AUC for adolescents in NUCB2020 was 5,414 ng•h/ml while steady state exposure levels in adults was cited as 4700 ng•h/ml in the package circular.

4. Analysis of Efficacy

The primary efficacy endpoint for NUCB2020 was the change in HBV DNA after 4 weeks of lamivudine treatment. The proportion of patients who received lamivudine oral solution and who had undetectable HBV DNA levels at day 28 is shown in Table 3. In addition, two of the 12 adolescents who received lamivudine one 100 mg tablet daily had undetectable HBV DNA on day 28. Therefore, the proportion of patients with undetectable plasma HBV DNA levels varied between treatment groups and ranged from 17% in adolescents receiving 100 mg daily to 64% in subjects receiving 4 mg/kg/bid. When the proportion of patients with undetectable HBV DNA levels was examined for differences by age, 53% (9/17) of children from 2 to 6 years of age had undetectable HBV DNA levels at day 28 compared to 39% (9/23) of children from 7 to 12 years of age and 17% (2/12) of adolescents. It is not clear why adolescent patients had a lesser response, but the sponsor states that it may have been due to poor compliance, to lower plasma HBV DNA levels on enrollment leaving less room for HBV DNA reductions, or to the small number of patients studied. Similar results were seen after the calculation of the log reduction of HBV DNA for each treatment group. While the 0.35 mg/kg/bid group and the 100 mg tablet daily group had mean log reductions in HBV DNA of 2.6 and 2.3 $\log_{10}$ respectively, the other three dosage groups had a reduction in HBV DNA levels of 3 $\log_{10}$ at day 28. Plasma HBV DNA values returned to baseline levels for all subjects who had had undetectable levels within four weeks of stopping treatment.

Secondary efficacy endpoints included the percentage of patients with normalized ALT values after four weeks of treatment with lamivudine. Only four patients (two in the 1.5 mg/kg/bid group, one in the 0.35 mg/kg/bid group, and one the 100 mg daily group) had ALT values that decreased to levels below the upper limit of normal with treatment, and ALT values for all four patients increased after study treatment was stopped. Changes in HBV serological markers were also examined. One patients in the 1.5 mg/kg/bid group lost HBeAg at week 12 and remained e antigen negative at 16 weeks. No patients developed antibodies to hepatitis e antigen, lost HBsAg, or developed antibodies to hepatitis surface antigen. Overall, no treatment response was noted in the analysis of secondary efficacy endpoints.

5. Analysis of Safety

All 53 patients were included in the safety analysis. No patients withdrew from this study due to adverse events. There were no deaths.

Clinical adverse events were reported in 36 (68%) children. Clinical adverse events reported in at least 10% of patients included malaise and fatigue (28%), ENT infection (17%), cough (15%), temperature change (11%), and headache (11%). Clinical adverse events judged to be drug related were reported in 11 or 21% of patients; malaise and fatigue was the only adverse event reported in at least 5% of children. Serious adverse events were reported in two patients. A 13 year old male with a history of emotional problems was diagnosed with a mood disorder on day 108, and a 12 year old in the 1.5 mg/kg/bid treatment group had a headache and loss of consciousness on day 52. Neither of these serious adverse events was considered to be drug related.

No changes in laboratory data were reported as adverse events. However, one patient reported a Grade 4 laboratory adverse event due to an elevation in CPK on day 112. Overall, 26 patients (49%) reported an abnormal ALT level at some time during the study; ALT elevation was described as Grade 1 in 25 patients and Grade 2 in one patient. Sixteen children had an elevated ALT reported during treatment compared to 24 patients with an abnormal ALT after treatment was terminated. When changes in ALT were compared to baseline values, one patient had an increase in ALT to more than twice baseline during treatment and four patients had increases in ALT to more than twice baseline after treatment. A Grade 2 increase in bilirubin was reported for one study subject and 7 patients had a Grade 3 elevation. Only one patient had an increase in ALT to more than twice baseline, a bilirubin value more than twice the upper limit of normal, and an increase in bilirubin to more than twice baseline. Although abnormal CPK levels were reported in 12 children (23%), 11 of the 12 had Grade 1 elevations only. Grade 1 neutropenia was noted in six children (11%).

Overall, lamivudine was well tolerated in NUCB2020. Neither unexpected adverse events or an increased incidence of adverse events were noted. No post-treatment increase in ALT or bilirubin levels was reported. However, the safety results of this study are of limited value because of the short duration of treatment.

6. FDA Analysis of Study NUCB2020

The interpretation of data from study NUCB2020 was limited by the small number of patients enrolled in each treatment group, by the short duration of treatment, and by the lack of supporting histologic data. Although there was a reduction of plasma HBV DNA levels in all age and dosage groups during treatment with lamivudine, less than one-half of patients in each treatment group developed undetectable HBV DNA levels and HBV DNA levels for all patients returned to baseline with the cessation of treatment. In addition, it is unclear why there was a lesser response in adolescents, and this lesser response is of concern. Finally, there was little appreciable effect of lamivudine on ALT levels or serologic markers. Overall, the results of this study provided information for dose selection and preliminary information on the antiviral activity of lamivudine.

Overall, lamivudine was well tolerated by patients in NUCB2020. All patients completed 28 days of treatment with the study drug. No patients discontinued the study because of adverse events, and there were no deaths. The majority of clinical adverse events were either consistent with the symptoms of hepatitis B (malaise and fatigue) or were typical of common childhood illnesses (ENT infections, cough, etc.). Clinical adverse events judged to be drug related were uncommon, and no serious drug-related clinical adverse events were reported. The most commonly reported laboratory adverse event was an increase in serum ALT. On review of the study data, 32 patients (60%) had an ALT value greater than the upper limit of normal at baseline, and ALT values remained elevated for all of these patients during the study. However, only 14 patients (26%) reported ALT levels more than twice the upper limit of normal during the study; these elevations were more commonly noted after study treatment was stopped; and the

maximum ALT reported was 157 IU/L. Although three patients with ALT values within normal limits at baseline had an increase in ALT to above the upper limit of normal during the study, these increases in ALT were mild, and no ALT values were higher than 42 IU/L.

7. Study Summary

This Phase II, open-label, multidose, multicenter trial was designed to study the pharmacokinetics, activity, and safety of lamivudine in the treatment of children and adolescents with chronic hepatitis B infection. Using pharmacokinetic and short term efficacy data, the applicant determined that lamivudine 3 mg/kg once daily was the appropriate dosage of lamivudine for the treatment of chronic hepatitis B infection in pediatric patients from two to 13 years of age. The lamivudine dosage for adolescents of 100 mg daily was chosen because of the similarity of the pharmacokinetic values for adolescents and adults at that dosage. Only limited information was obtained about the antiviral activity of lamivudine because of the small sample size, the multiple treatment groups, and the short duration of treatment. It was of concern that adolescents had a lesser response to treatment than younger children, and the reason for this lesser response is unknown. Lamivudine was well tolerated in this study and no new safety concerns were noted in NUCB2020.

B. Study NUC30903

NUC30903, "A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of 52 weeks lamivudine treatment at a dose in 3 mg/kg in paediatric subjects with chronic hepatitis B." was a 52 week study of lamivudine compared to placebo in the treatment of children from two to 17 years of age infected with chronic hepatitis B infection. The first subject was enrolled in this study in October 1998 and the last subject completed the study in July 2000. A Clinical Study Report containing the 52 week safety and efficacy data from NUC30903 was submitted with this supplemental New Drug Application on February 27, 2001.

1. Study Design

NUC30903 was a double-blind, placebo controlled, multicenter trial in which children with chronic HBV infection were randomized to receive 52 weeks of either lamivudine oral solution (3 mg/kg once daily) or placebo. Study NUC30903 was designed to enroll 255 subjects who were to be randomized to lamivudine or placebo in a 2:1 ratio. Eligible subjects were from two to 17 years of age with chronic hepatitis B infection, with liver biopsy evidence of inflammation, and with baseline ALT values of 1.3 times the upper limit of normal or greater. The diagnosis of chronic HBV infection was based on a positive hepatitis B surface antigen for six months prior to study screening, positive hepatitis B e antigen, and detectable plasma HBV DNA by the [redacted] assay (with a lower limit of detection of 0.7 MEq/ml). Patients could not have signs of decompensated liver disease, have received interferon within 12 months of study entry, or have coinfection with hepatitis C or human immunodeficiency virus. The primary

efficacy endpoint was the proportion of patients achieving a complete virologic response which was defined as a negative HBeAg and undetectable HBV DNA at week 52. Secondary efficacy endpoints included the proportion of patients with a sustained ALT response (at least two consecutive ALT measurements equal to or less than the upper limit of normal and maintained to week 52), the proportion of patients with HBeAg seroconversion (negative HBeAg and positive HBeAb), the percentage of patients with undetectable HBV DNA levels at week 52, and the proportion of patients with HBsAg loss and detectable HBsAb. Safety data were collected as a tabulation of reported adverse events. Study subjects were evaluated at screening, at baseline, and at weeks 2, 4, 8, 16, 24, 32, 40, 48, and 52. After week 52, subjects in study NUC30903 were eligible to enroll in study

2. **Study Population**

A total of 288 children were enrolled in NUC30903. The median age was 9.0 years with an age range of one to 17 years. When the age strata used in NUCB2020 were applied to this study population, there were 89 children from one to six years of age, 126 children from seven to 12 years of age, and 73 adolescents from 13 to 17 years of age. The majority of patients were male (64%). Most children were White (69%) or Asian (20%). Thirty-four percent of patients acquired hepatitis B perinatally, 8% acquired HBV through family contact, 6% had community acquired HBV, and the mode of acquisition was unknown for 45%. Overall, the two treatment groups were similar with regard to demographic characteristics, except the time since diagnosis of hepatitis B was slightly longer for children in the lamivudine group (4.0 years) compared to the placebo group (3.2 years).

Baseline laboratory and histopathologic characteristics related to hepatitis B infection are shown in Table 3.

Table 3: Baseline Laboratory Assessments for Patients in NUC30903 (Modified Intent-to-Treat Population)

	Placebo	Lamivudine
Mean HBV DNA (Meq/ml)	1884.0	2145.1
Mean ALT (/ULN)	3.2	2.7
Mean Bilirubin (/ULN)	0.4	0.4
Mean Knodell HAI Score	5.7	4.7
Mean Knodell HAI Necroinflammatory Score	4.3	3.5
Mean Ishak Score	7.2	5.8
Mean Ishak Necroinflammatory Score	5.2	4

Source: Study NUC30903, CSR, Volume 8.4, Pages 57 and 59.

Although the mean HBV DNA level was higher in the lamivudine group, the median value was actually higher for children receiving placebo. The ALT and bilirubin values were similar between the two groups. The Knodell and Ishak scores from pretreatment liver biopsies were determined by a central pathologist blinded to the assigned treatment group. There was a statistically significant difference between the scores of the two groups; both the total scores and the scores assessing inflammation and necrosis were higher in the placebo group than in the lamivudine group. A total of 129 patients had previously been treated with interferon including 40 of 96 (42%) patients in the placebo group and 89 of 191 (47%) in the lamivudine group. In addition, eight patients had previously been treated with lamivudine for hepatitis B (two in the placebo group and six in the lamivudine group). Finally, nine additional patients received antiviral or anti-inflammatory drugs to treat hepatitis B; these drugs included prednisone, famciclovir,

3. Patient Accounting

A total of 288 children were enrolled in NUC30903 and randomized to receive either placebo or lamivudine (3mg/kg/day). The number of patients randomized to each treatment group and included in each study population are shown in Table 4. The primary population for the analysis of efficacy was the modified intent-to-treat population which included randomized patients with a confirmed diagnosis of chronic hepatitis B. The as treated population included patients with no clear evidence of failure to take their study medication; this was a primary population for the evaluation of safety and a secondary population for the determination of efficacy. Finally, the evaluable population included randomized patients with no major protocol violations; this population also served as a secondary population for the evaluation of efficacy.

Table 4: Study Populations in NUC30903

	Placebo	Lamivudine	Total
All Randomized	97	191	288
Modified ITT	95	191	286
As Treated	96	191	287
Evaluable	92	181	273

Source: Study NUC30903. CSR. Volume 8.4, Page 54.

Two subjects were randomized but not included in the modified intent-to-treat population because they did not have a confirmed diagnosis of chronic hepatitis B infection; one of these patients did not have positive hepatitis B surface antigen documented for six months prior to study entry and the other was HBeAg negative at baseline. Only one randomized patient was excluded from the as treated population; consent for study participation was withdrawn for this child before he received study drug. Five placebo subjects and ten lamivudine subjects were excluded from the evaluable population because of protocol violations or early withdrawal from the study. Protocol violations included no confirmed diagnosis of chronic hepatitis B infection (2 subjects) and receipt of contraindicated antiviral medications (7). The remaining children were excluded because of loss to follow-up (2), noncompliance (1), consent withdrawn (1), and adverse

events (one patient with severe bruising and one with an increased ALT). There were six additional children who had protocol violations but who were included in the evaluable population; five of these children had ALT values which were within normal limits at baseline and one child was one year of age.

4. **Analysis of Efficacy**

The primary efficacy endpoint for NUC30903 was the proportion of patients with a complete virologic response (CVR) at 52 weeks; the primary population for the analysis of efficacy was the modified intent-to-treat population. Complete virologic response, defined as loss of detectable serum HBeAg and undetectable HBV DNA serum levels by the [redacted] assay (lower limit of detection = 0.7 MEq/ml), was noted in 44 of 191 (23%) patients receiving lamivudine and 12 of 95 (13%) receiving placebo (p=0.037). In the analysis of the CVR, missing data were treated as failure; but when the last observation was carried forward, no change in response rate was noted: 23% of lamivudine subjects and 13% of placebo subjects achieved a CVR. The CVR at week 52 for the evaluable population was also similar with 24% of lamivudine subjects and 13% of placebo subjects attaining a CVR (p=0.037). The primary endpoint was also examined with all data outside of the week 52 visit window excluded and missing data counted as failures. In this analysis, the CVR was 24% (28/119) for the lamivudine group but dropped to 10% (6/62) for the placebo group. Investigators inadvertently received HBeAg results for 24 subjects receiving lamivudine and 14 receiving placebo; per protocol investigators were to be blinded to these results until week 48. However, the investigators remained blinded to the treatment group for each of these subjects. When the CVR was analyzed with these subjects excluded, the CVR was 11% for placebo subjects and 23% for lamivudine subjects. Finally, CVR was analyzed by the week of the study. In both groups, there was a gradual increase in the proportion of subjects achieving a CVR until week 48. Between week 48 and week 52, nine lamivudine subjects lost the CVR and five achieved a CVR. In contrast, two placebo patients lost and two gained a CVR; this included one patient counted as a failure because of missing data. The applicant did not explain the reason for the relatively large number of subjects (9) in the lamivudine treatment group with a change in CVR response between weeks 48 and 52.

The proportion of study subjects achieving a complete virologic response was also determined for treatment differences according to baseline HBV disease. After analyses of CVR using logistic regression analysis models, there was a treatment difference noted in CVR by baseline ALT and baseline HAI scores. On further analyses, patients with an elevated ALT or a Knodell HAI score of 5 to 9 on a prestudy liver biopsy were more likely to achieve a CVR. The proportion of subjects with a CVR increased with increasing ALT levels at baseline; 8% of placebo and 12% of children with baseline ALT level less than two times the upper limit of normal achieved a CVR compared to 24% of placebo and 50% of lamivudine subjects with baseline ALT values more than five times the upper limit of normal. Additional subgroup analyses of CVR, revealed a difference in treatment effect for patients with increased baseline HBV DNA levels. A greater number of patients in both treatment groups with HBV DNA levels less than 800 MEq/ml at

baseline achieved a CVR than those with baseline HBV DNA levels greater than 800 MEq/ml. While 26% of placebo and 32% of lamivudine recipients with HBV DNA levels less than 800 MEq/ml had a CVR, only 2% of placebo subjects and 14% of lamivudine subjects with a HBV DNA level greater than 800 MEq/ml had a CVR.

Additional analyses were performed to examine the effect of age and weight at baseline, ethnic origin, and country on the proportion of subjects achieving CVR. Although this study was not powered to test for any treatment differences by subgroup, differences in treatment effect were similar for each of these subgroups except baseline age as shown in Table 5.

Table 5: Analysis of CVR by Age for Subjects in NUC30903

Age (years)	Placebo	Lamivudine
2 – 6	3/38 (8%)	16/49 (33%)
7 – 12	5/31 (16%)	20/95 (21%)
13 - 17	4/26 (15%)	8/47 (17%)

Source: Study NUC30903, CSR, Volume 8.4, Table 17.

In order to explain the association between age and treatment, the applicant also analyzed CVR using logistic regression modeling and found that baseline variables such as HBV DNA levels, ALT values, and Knodell scores confounded the results. The applicant also examined the effect of age on HBV DNA response and ALT normalization, and no statistically significant difference was noted with respect to either of these endpoints. Therefore, the applicant concluded that the relationship between age and CVR could not be determined.

According to the study protocol, the most important secondary efficacy endpoint was the sustained ALT response, defined as at least two consecutive ALT values less than the upper limit of normal and maintained through to week 52 without any ALT measurements greater than the upper limit of normal. A sustained ALT response at week 52 was seen in 11 of 88 (13%) placebo subjects and in 100 of 183 (55%) lamivudine subjects ($p < 0.001$). The sustained ALT response was commonly seen in subjects with a CVR at week 52. Nine of 11 placebo subjects with a CVR and 36 of 43 lamivudine subjects reaching a CVR at week 52 had sustained normalization of ALT. In addition, the majority of subjects in both treatment groups with undetectable HBV DNA levels also had a sustained ALT response. Therefore, a sustained ALT response was commonly seen in subjects who showed a treatment benefit as measured by other endpoints. When the ALT response was examined using a broader definition, i.e., a decrease in ALT to measurements at or below the upper limit of normal for at least one visit, 15 of 88 (17%) placebo subjects and 113 of 183 (62%) lamivudine subjects showed an ALT response at week 52. Although ALT responses were seen as early as four weeks, the median time to ALT response in the lamivudine group was 24 weeks. It should be remembered that unlike with the sustained ALT response, ALT response was not necessarily maintained through the 52 weeks of the study.

As shown in Table 6, changes in several different serologic markers of response were analyzed as secondary efficacy endpoints.

Table 6: Summary of Serologic Responses for Subjects in NUC30909

Serologic Response	Placebo	Lamivudine	P value
Neg HBeAg / Pos HBeAb / neg HBV DNA	12/95 (13%)	42/191 (22%)	0.057
Neg HBeAg / Pos HBeAb	14/95 (15%)	48/191 (25%)	ND
HBeAg loss	14/95 (15%)	50/191 (26%)	0.029
HBsAg loss	0/95	3/191	ND
Neg HBsAg / Pos HBsAb	0/95	0/191	ND

Source: Study NUC30903, CSR, Volume 8.4, pages 70 - 76.

As noted above, HBeAg loss was fairly uncommon and seen in only 15% of placebo and 26% of lamivudine subjects. As a result, three component seroconversion (negative HBeAg, positive HBeAb, and negative HBV DNA at week 52) and two component seroconversion (negative HBeAg and positive HBeAb at week 52) were reported in a small number of subjects receiving either lamivudine or placebo. However, the proportion of subjects with a response to each of these serologic endpoints was higher for patients receiving lamivudine than for those who received placebo. It was notable that the proportion of subjects in both treatment groups achieving three component seroconversion or HBeAg loss increased as the baseline ALT values increased. Finally, only three subjects, all in the lamivudine treatment group, lost HBsAg and no subjects developed antibodies to hepatitis B surface during this study.

A decrease in HBV DNA levels to undetectable (less than 0.7 MEq/ml by the [redacted] assay) was noted in 16% (15/95) of subjects who received placebo compared to 61% (117/191) of those who received lamivudine ($p < 0.001$). Although the median HBV DNA values decreased for patients in both treatment groups over the 52 week study, the median reduction in HBV DNA at week 52 was 51.7% for placebo subjects and 99.9% for lamivudine subjects. While a smaller number of subjects in the placebo group had undetectable levels of HBV DNA during the study, HBV DNA levels also decreased over time for these patients.

When the HBV DNA response was examined by week of study, HBV DNA levels decreased to undetectable early in the study for most lamivudine recipients; 70% of lamivudine subjects had at least one HBV DNA value which was undetectable by week 4. The peak HBV DNA response occurred at week 16; 71% of lamivudine subjects had undetectable HBV DNA at that time point, while fewer subjects in the lamivudine group had a HBV DNA response at week 52 (61%). HBV DNA breakthrough was analyzed by the applicant. Twenty-six percent of subjects had reemergence of detectable HBV DNA levels after at least two measurements with HBV DNA levels less than the lower limit of quantification of the [redacted] assay. Of the subjects with HBV DNA breakthrough, 47% had YMDD variant HBV identified at week 52. Many of the breakthroughs appeared late in the study and HBV DNA levels were still low at week 52; additional data is needed in order to determine if the HBV DNA levels continued to rise

after week 52. In addition, approximately one-half of the subjects with reemergence of HBV DNA also had increases in ALT values.

In conclusion, the primary efficacy endpoint for NUC30903 was the proportion of subjects with a complete virologic response at week 52; this response was seen in 13% of placebo recipients and 23% of lamivudine recipients (p=0.037) and was confirmed with several different analyses (last observation carried forward, evaluable population, on schedule data). Additional analyses revealed that the proportion of patients achieving a CVR was influenced by the baseline ALT level, baseline DNA level, and baseline HAI score. In subgroup analyses, fewer adolescents achieved a complete virologic response than children in the two younger age groups. On analyses of secondary efficacy endpoints, the proportion of subjects with normalization of ALT and undetectable HBV DNA levels at week 52 were substantially higher for patients in the lamivudine treatment group. However, the proportion of subjects with undetectable HBV DNA levels did peak early in the study and decreased slowly over time. Fewer subjects in either treatment group experienced HBeAg or HBsAg seroconversion, but the proportion showing a treatment response for any serologic endpoint was higher in the group of children receiving lamivudine. Overall, a treatment effect was seen in children with chronic hepatitis B infection receiving lamivudine 3 mg/kg daily to a maximum of 100 mg, but concerns about baseline characteristics which might identify children with a greater treatment effect, about the efficacy of lamivudine in adolescents, and about the rebound increase in HBV DNA were raised.

5. **Analysis of Safety**

The primary population for the safety analysis of study NUC30903 was the as treated population which was defined as the population with no clear evidence of failure to take study drugs. This population included 287 patients; one patient was randomized but not included in the as treated population, because his parents withdrew consent prior to his receiving study drugs. The median duration of exposure, 367 days, was provided for the modified intent-to-treat population but not the as treated population.

There were no deaths during the study. Two study subjects withdrew due to adverse events, but there were no study discontinuations due to serious adverse events. Patient 36293, a 16 year-old male receiving placebo, withdrew because of an increased ALT to 1059 U/L at week 32. His ALT decreased to 88 U/L by the next study visit six weeks later. The second patient was a eight year-old receiving lamivudine whose parents stopped his study drug because of severe bruising and prolonged bleeding after a laceration of his finger. Although this adverse event was judged as possibly drug related, the patient had a history of emotional illness, and the investigators were concerned that his injuries were self inflicted.

Adverse events were reported in 89% (85/96) of placebo subjects and 78% (149/191) of lamivudine subjects. Data concerning clinical adverse events were provided by organ system, by type of adverse event, and for individual patients. Adverse events involving the ear, nose and throat were the most frequent adverse events reported by organ system

and occurred in 67% of placebo and 47% of lamivudine subjects. This was largely due to the high number of ENT infections, which were reported in 26% of placebo and 17% of lamivudine subjects. Other clinical adverse events reported in more than 10 % of each treatment group included cough, increased temperature, headache, and abdominal pain or discomfort. Each of these was reported in a similar proportion of lamivudine and placebo subjects except for cough; which was reported more commonly in the lamivudine group (25% compared to 15% in the placebo group). Adverse events were also presented by age, gender, and ethnic origin. No differences were apparent between these groups except for an increased incidence of ENT infections in the younger children and an increased incidence of viral infections in older children.

Clinical adverse events considered to be drug related by the investigator were reported in 36 of 96 (38%) of patients receiving placebo and in 59 of 191 (31%) of patients receiving lamivudine. Drug-related adverse events reported by organ system most commonly involved the gastrointestinal system; drug-related adverse events for other organ systems were reported in less than 10% of patients in either treatment group. The individual types of drug-related clinical adverse events reported in more than 3% of subjects are shown in Table 7.

Table 7: Drug-Related Clinical Adverse Events with a Greater than Three Percent Incidence Rate Reported in Either Treatment Group of NUC30903

Drug-Related Adverse Event	Placebo	Lamivudine
Abdominal Discomfort and Pain	8 (8%)	8 (4%)
Headache	5 (5%)	11 (6%)
Malaise and Fatigue	3 (3%)	7 (4%)
Nausea and Vomiting	3 (3%)	6 (3%)
Skin Rashes	2 (2%)	6 (3%)
Pharyngitis	4 (4%)	4 (2%)
Feeding Problem	4 (4%)	2 (1%)
Diarrhea	2 (2%)	5 (3%)

Source: Study NUC30903, CSR, Volume 8.4, Table 47.

As shown in Table 7, drug-related clinical adverse events reported by individual type of event were uncommon and none were reported in more than 8%. In addition, the incidence of individual drug-related clinical adverse events was similar in the placebo and lamivudine treatment groups.

Ten serious clinical adverse events were reported in seven patients. Although all of these patients received lamivudine, none of these serious adverse events was considered to be drug-related. The serious clinical adverse events included new-onset seizure disorder, meningitis, laceration, asthma exacerbation, abdominal pain, appendicitis, bronchitis, carbon monoxide exposure with resultant bronchitis, erythema multiforme following ceclor administration, and lamivudine overdose. A 12 year-old female who took 200 ml of lamivudine was treated with gastric lavage but did not develop symptoms attributable to lamivudine toxicity.

Laboratory adverse events involving the hepatobiliary tract and pancreas were reported as organ system events. Abnormal liver function tests were reported in 5% of subjects in each treatment group, and abnormal pancreatic enzymes were reported in 3% of placebo subjects and less than 1% of lamivudine subjects. The incidence of abnormal liver function tests for different subgroups is shown in Table 8.

Table 8: Incidence of Abnormal Liver Function Tests for Subgroups in NUC30903

Age	**Placebo**	**Lamivudine**
2 – 6 years	1 (3%)	6 (10%)
7 – 12 years	1 (3%)	5 (5%)
13 – 17 years	3 (12%)	0
Gender		
Female	4 (11%)	3 (4%)
Male	1 (2%)	1 (<1%)
Ethnic Origin		
Asian	4 (17%)	2 (6%)
White	1 (2%)	5 (4%)

Source: Study NUC30903, CSR, Volume 8.5, Supporting Tables 26, 27, and 28.

As shown in Table 8, the incidence of abnormal liver function tests in subjects receiving lamivudine appeared to be higher for the youngest children and no abnormal liver function tests were reported for adolescents receiving lamivudine. Females in both treatment groups had a higher incidence of abnormal liver function tests than males. Finally, Asians in both treatment groups had a higher incidence of abnormal liver function tests than White subjects. Other ethnic groups were not included in this table because of the small number of patients in each group. The incidence of abnormal pancreatic enzymes was similar for the different subgroups examined.

Abnormal liver function tests were also described as the number of subjects reporting Grade 3 and Grade 4 laboratory abnormalities in ALT, as time to development of Grades 3 and 4 ALT elevations, and as number of subjects with specific abnormalities in ALT. Overall, Grade 3 abnormalities in ALT occurred in 7 (7%) placebo subjects and 13 (7%) lamivudine subjects; only one subject, a placebo recipient, reported a Grade 4 ALT abnormality. Fluctuations of ALT were common in both treatment groups with isolated increases in ALT followed by return to baseline values. Increased ALT values occurred at all time points for subjects in the placebo treatment arm; however, increases in ALT measurements were more likely to occur early during treatment (weeks 4 or 8) in the lamivudine arm. Few children in either group had ALT elevations more than twice baseline values. Increases in ALT to more than twice the baseline value were reported in 28% of placebo subjects and 19% of lamivudine subjects. ALT values decreased over time for subjects in both treatment groups, but the decrease in ALT was greater for subjects in the lamivudine arm. While the median ALT value for patients in the lamivudine group changed from 2.1 times the upper limit of normal at baseline to 0.8 times the upper limit of normal at week 52, the median ALT changed from 2.3 times the upper limit of normal at baseline to only 1.7 times the upper limit of normal in placebo subjects. However, it is difficult to discern any post-treatment hepatic flares for subjects

in the lamivudine group since data provided in the Clinical Study Report included ALT values to week 52 only.

Summary statistics for percentage change over the 52 week study for albumin, white blood cell count, hemoglobin, platelets, neutrophils, amylase, lipase, bilirubin, and creatinine phosphokinase showed little change between baseline and week 52 for subjects in both treatment groups. Grade 3 and 4 abnormalities were reported in albumin (one placebo subject with a Grade 3 increase), amylase (Grade 3 increase in one patient in each treatment group), bilirubin (one lamivudine subject with a Grade 3 increase), CPK (two placebo subjects with a Grade 3 increase, three placebo subjects with a Grade 4 increase, and two lamivudine subjects with a Grade 4 increase), and lipase (one lamivudine subject with a Grade 3 increase). Although there were a significantly higher number of patients with Grade 3 or 4 increases in CPK in the placebo group, the incidence of other Grade 3 and 4 laboratory abnormalities were similar between the two treatment groups.

In summary, no unexpected clinical or laboratory adverse events were reported in children receiving lamivudine for 52 weeks to treat chronic hepatitis B infection, and most clinical adverse events represented signs or symptoms of common childhood illnesses. The incidence of drug-related adverse events was similar in the placebo and lamivudine groups. ALT elevations occurred in a similar percentage of lamivudine and placebo subjects; however, data past 52 weeks was not provided, so it cannot be determined if any lamivudine subjects developed post-treatment adverse events including hepatic flares.

6. Analysis of HBV YMDD Genotypic Results

Genotypic analysis was used to detect the incidence of YMDD variant HBV at baseline and at week 52. YMDD detection was completed in 89% of placebo and 91% of lamivudine subjects at baseline and in 90% of placebo and 87% of lamivudine subjects at week 52. Virus was not amplified by PCR in 7 (8%) placebo and in 52 (31%) lamivudine subjects. YMDD mutations were found in 30/166 (18%) lamivudine subjects at week 52. YMDD-postive HBV was isolated from one placebo subject at week 52, however, the applicant expressed concern that the blood sample for resistance testing had been mislabeled.

When the demographic characteristics of lamivudine subjects with HBV containing YMDD mutations were compared to those of lamivudine subjects with HBV isolated but no YMDD mutations, the subjects who had YMDD-positive virus were younger and smaller. The median age for subjects with resistant virus was 7.0 years compared to 9.0 years for subjects without HBV YMDD mutations, and the average weight and height were also lower. Few differences were noted in the baseline laboratory values for subjects with and without YMDD mutations except for differences in baseline HBV DNA levels. The median HBV DNA level for subjects with YMDD-negative HBV was 777 MEq/ml compared to 1,626 MEq/ml in the YMDD-positive group.

Efficacy results for lamivudine recipients with YMDD positive and negative HBV are shown in Table 9.

Table 9: Efficacy Results for Lamivudine Recipients with and without YMDD-Containing HBV Variants

Efficacy Result at 52 Weeks	Non-Variant HBV	Variant HBV
Complete Virologic Response	40/136 (29%)	0/30
Sustained ALT Response	78/129 (60%)	14/30 (47%)
3 Component Seroconversion	39/136 (29%)	0/30
2 Component Seroconversion	43/136 (32%)	1/30 (3%)
HBeAg Loss	44/136 (32%)	1/30 (3%)
Undetectable HBV DNA	94/136 (69%)	9/30 (30%)
ALT <ULN	90/136 (70%)	14/30 (47%)

Source: Study NUC30903. CSR. Volume 8.4, Pages 94-98.

No subjects with YMDD-positive HBV isolated by PCR at week 52 had a complete virologic response or three component seroconversion (loss of HBeAg, gain of HBeAb, and undetectable HBV DNA). Only one subject with YMDD positive HBV had two component seroconversion (loss of HBeAg with gain of HBeAb) or loss of HBeAg. Nine subjects with YMDD variant HBV identified by PCR had undetectable HBV DNA by [redacted] assay. HBV DNA levels at baseline and at week 52 were also compared between patients with and without variant virus. In patients with YMDD-negative virus, median HBV DNA levels decreased from 777 MEq/ml at baseline to 0.35 at week 52; for patients with YMDD-positive HBV, DNA levels decreased from 1626 to 2.7 MEq/ml. It should be noted that 0.35 MEq/ml was an assigned value for undetectable HBV DNA levels and represented one-half of the threshold value of the [redacted] assay. Week 52 HBV DNA levels in patients with YMDD-positive HBV were lower than those of subjects in the placebo group (538 MEq/ml at week 52). HBV DNA levels in patients with YMDD-positive HBV began to increase at week 48 and had increased further at week 52. Since HBV DNA data was not provided past 52 weeks, it is not known if HBV DNA levels for patients with YMDD-positive HBV continued to increase until reaching baseline values or values similar to those seen in the placebo group. Although almost one-half of the subjects in the YMDD-positive group had a sustained ALT response or an ALT value less than the upper limit of normal at week 52, the response was substantially better for subjects with YMDD-negative HBV. When the presence or absence of YMDD variant HBV and efficacy endpoints were analyzed using logistic regression models, there was a negative correlation with YMDD variants and all efficacy endpoints. When the efficacy results for subjects with YMDD-positive HBV on lamivudine were compared to those of placebo recipients, the only significant difference was that a higher proportion of subjects with YMDD variant HBV than placebo recipients had a sustained ALT response. When YMDD-positive and negative subjects within the lamivudine treatment group were compared, YMDD-negative subjects had a substantially better response in two component seroconversion and HBeAg loss. The applicant concluded that HBeAg responses were not seen as frequently in subjects with YMDD-positive HBV, but that these subjects exhibited improvement in HBV DNA and ALT levels which was similar to the results noted in YMDD-negative subjects.

The overall incidence of adverse events was similar for YMDD positive and negative subjects. However, the incidence of drug-related adverse events was higher in the YMDD-positive group (43% compared to 27% for the YMDD-negative group). Although the numbers were small and it was difficult to determine specific differences between the two groups, there was a higher incidence of headache, nausea and vomiting, and malaise and fatigue in the YMDD-positive group. The incidence of Grade 3 and Grade 4 laboratory adverse events was lower for subjects in the YMDD-positive group. Two subjects had Grade 3 laboratory adverse events (both with ALT elevations), but no Grade 4 laboratory adverse events were reported in YMDD-positive subjects. When ALT abnormalities were compared between YMDD-negative and YMDD-positive subjects, the incidence of ALT values either two or three times the upper limit of normal were similar for both groups. A greater overall decrease in ALT values was noted for YMDD-negative subjects at week 52 than for subjects with YMDD-positive HBV; the percentage decrease from baseline was 61.3% for the non-variant group and 43.2% for the YMDD variant group.

Eighteen percent of subjects treated with lamivudine developed YMDD variant HBV. YMDD mutations were seen more commonly in younger and smaller subjects and in subjects with higher baseline HBV DNA levels. Fewer subjects with YMDD-positive HBV had a complete virologic response and after logistic regression modeling, the presence of YMDD variants negatively correlated with every efficacy endpoint. Differences in HBeAg loss were particularly notable and lesser differences were noted in the HBV DNA and ALT response. Although there was a higher incidence of drug-related adverse events in the group of subjects with YMDD-positive HBV, no specific safety concern was noted for subjects with YMDD variant virus. Finally, the clinical study report for NUC30903 did not contain information past week 52 of the study, so it is not known if the efficacy and safety results in subjects with YMDD mutations changed during continued follow-up.

7. FDA Analysis of Efficacy

a. Primary efficacy endpoint (complete virologic response)

The primary efficacy endpoint in study NUC30903 was the proportion of subjects with complete virologic response (CVR) at week 52; CVR was defined as loss of HBeAg with undetectable HBV DNA by the [redacted] assay. By protocol criteria, CVR was performed for the modified intent-to-treat population, missing data were counted as failures, and only data from the week 52 visit were acceptable. In the applicant's analyses, a CVR was seen in 23% of lamivudine subjects and 13% of placebo subjects. Little change in the results was seen when CVR was analyzed for other populations, if patients who had received lamivudine before study enrollment were excluded, or if the definition of week 52 data was narrowed. However, when a slightly larger time window for the week 52 visit was used to include three patients who were lost to follow-up at 52 weeks, the proportion of subjects with CVR was 45/191 (24%) for lamivudine subjects and 14/95 (15%) for the placebo subjects. Although the change in proportion of subjects

with CVR only changed slightly, the p-value changed from 0.037 to 0.085. Although this changes the p value to one greater than 0.05, a p value of .085 is still suggestive of a real treatment effect (see Dr. Hammerstrom's review). In addition, the original p value of 0.037 was determined using strict criteria which were defined prestudy in the protocol for NUC30903, and the slightly higher p value was only obtained after additional sensitivity analyses by the FDA reviewers.

Between weeks 48 and 52, nine subjects receiving lamivudine "lost" their CVR as compared to only three subjects in the placebo group. (One additional placebo subject lost the CVR because of missing data at week 52). Three lamivudine subjects were HBeAg negative at week 48 but positive at week 52; six lamivudine subjects with undetectable HBV DNA levels at week 48 had detectable HBV DNA at week 52. It is unclear why these subjects lost their HBeAg or HBV DNA response; but for two of these nine patients (one who lost the HBeAg response and one who lost the HBV DNA response) the loss of response may have been due to the development of YMDD-positive HBV which was detected at week 52. The CVR at week 48 for subjects in the lamivudine group was 27%, and after these unexplained changes in CVR for nine subjects fell to 24%. The CVR for subjects receiving placebo was 14% at week 48 and at week 52. Therefore, widening the window to week 48 for analysis of CVR results in an increase in the response rate for subjects in the lamivudine group but not in the placebo group.

These changes highlights the difficulties with the use of CVR as the primary efficacy endpoint. The only widely accepted surrogate marker in the study of the treatment of chronic hepatitis B is the examination of hepatic tissue pre and post treatment. Although children frequently have a liver biopsy during the diagnostic work-up for chronic hepatitis B infection, it would be ethically difficult to obtain repeat liver biopsies after treatment in children. Neither investigators nor parents would be willing to consent to a procedure which is not without risk in a child who was doing well clinically. Therefore, efficacy studies of the treatment of pediatric chronic hepatitis B infection must use other less reliable endpoints as surrogate markers. CVR was used as the primary efficacy endpoint in the study, but change in liver histopathology was used in adult trials forming the basis for approval of Epivir-HBV (see Dr. Styrt's review). In the adult trials, the proportion of subjects receiving lamivudine with a histologic response (defined as a 2 point or greater decrease in Knodell score) ranged from 52 – 56% compared to a response rate of 23 – 25% in placebo subjects. HBV DNA levels using a solution hybridization assay for lamivudine treated adults in these studies were undetectable in up to 98% of subjects at week 52, but the proportion of adults with loss of HBeAg at week 52 was only 17 to 32%. In summary, neither the changes in HBV DNA or in HBeAg at week 52 were ideal correlates for the histologic response noted in lamivudine treated subjects in clinical trials of adults. Therefore, CVR, the primary efficacy endpoint in the protocol for NUC30903, may not have accurately reflected the effect of lamivudine on liver tissue which is thought to be the most appropriate surrogate marker for chronic hepatitis B infection – much less on the long term outcome for children with hepatitis B. Consequently, not only should the proportion of children with CVR be examined closely, but results for secondary efficacy endpoints must also be considered carefully.

b. Secondary efficacy endpoints

Sustained ALT responses at week 52 were identified as the most important secondary efficacy endpoint in the protocol for study NUC30903 and may serve as a marker for the degree of liver inflammation. In this study, 13% of placebo recipients and 55% of lamivudine recipients had a sustained ALT response at week 52 ($p<0.001$). The number of subjects with sustained ALT response increased slowly over time and were seen in slightly over one-fourth of lamivudine recipients at week 24. The proportion of subjects with sustained ALT response peaked at week 48 (55%) and that percentage was maintained at week 52. Subjects in either treatment group with a CVR, a HBV DNA response, or HBeAg loss frequently also had a sustained ALT response. However, because changes in serologic endpoints were relatively uncommon, many subjects with a sustained ALT response did not have a CVR or loss of HBeAg. Finally, the proportion of children in NUC30903 with a sustained ALT response was similar to the response rate reported in clinical trials of adults (see Dr. Styrt's original NDA review).

As seen in Table 6, relatively few children receiving lamivudine experienced loss of either hepatitis e or hepatitis surface antigen and fewer still had appearance of hepatitis e antibody or surface antibody. However, subjects in the lamivudine arm did have higher response rates than children in the placebo arm for every secondary efficacy endpoint involving serologic markers, and similar response rates were reported in the original NDA review for adult subjects receiving lamivudine for the treatment of chronic hepatitis B infection. See Table 10 for a comparison of serologic response rates for children and adults.

Table 10: Response to Serologic Endpoints for Children Participating in NUC30903 Compared to Adult Subjects Participating in Previously Reviewed Phase III Studies

Serologic Response	Children in NUC30903		Adults in Phase III Trials[1]	
	Placebo	*Lamivudine*	*Placebo*	*Lamivudine*
Neg HBeAg / Pos HBeAb / neg HBV DNA	13%	22%	6%	17%
Neg HBeAg / Pos HBeAb	15%	25%	13%	18%
HBeAg loss	15%	26%	7 – 11%	17 – 33%
HBsAg loss	0	1.6%	0	0 – 4%

[1] Proportion of patients reported for these trials were obtained from Tables 1, 7, 15, and 19 of Dr. Styrt's NDA review of 21-003 and 21-004 and reflect response rates in four studies (NUCA3010, NUCAB3011, NUCB3009, and NUCB3010). The source for data from study NUC30903 was volume 8.4 of the CSR, pages 70-76.

Although there were important differences in the study design, methodology, and patient populations in the adult trials of lamivudine and study NUC30903, data presented in Table 10 show that response to serologic endpoints was similar between children participating in study NUC30903 and adults participating in Phase III clinical trials of lamivudine.

A greater response to serologic endpoints was seen in subjects with higher baseline ALT values. There was no difference in response to serologic endpoints at week 52 for children in the lamivudine and the placebo group when children had normal baseline ALT values. However, striking differences were noted were noted if baseline ALT values were greater than the upper limit of normal as shown in Table 11.

Table 11: Effect of Baseline ALT Values on Response Rates to Selected Serologic Endpoints

Baseline ALT	3 component seroconversion		HBeAg Loss	
	Placebo	Lamivudine	Placebo	Lamivudine
≤ ULN	1/7 (14%)	1/8 (13%)	1/7 (14%)	1/8 (13%)
> 2X ULN	9/58 (13%)	31/97 (32%)	10/58 (17%)	38/97 (39%)
> 5X ULN	4/17 (24%)	8/16 (50%)	4/17 (24%)	8/16 (50%)

Source: Study NUC30903, CSR, Volume 8.4, Tables 23 and 29.

Results shown in Table 11 suggest that children with chronic hepatitis B infection but normal ALT values should not be treated with lamivudine and that children with higher ALT values will show a greater treatment benefit. However, patient numbers are small and this study was not statistically powered to show differences in subgroup populations, so further study should be done to verify these results.

The effect of lamivudine treatment on HBV DNA levels was measured by the median decrease in HBV DNA levels over the study, by the percentage of subjects with at least one undetectable HBV DNA value, and by the proportion of subjects with undetectable HBV DNA at week 52. The median decrease in HBV DNA was 99.9% for subjects in the lamivudine group and 51.7% for subjects in the placebo group. Ninety-two percent of lamivudine subjects and 23% of placebo recipients had at least one HBV DNA measurement which was undetectable. The majority of lamivudine recipients (61%) had sustained undetectable HBV DNA levels at week 52 while only 16% of placebo recipients had undetectable levels at week 52 ($p<0.001$). This decrease in HBV DNA occurred early and peaked at week 16 (135 lamivudine subjects or 74% undetectable) and then HBV DNA levels slowly increased. In fact, 26% of subjects with undetectable HBV DNA levels on at least two visits had reemergence of HBV DNA. This commonly occurred late in the study and was often accompanied by an increase in ALT values. Almost one-half of the subjects had YMDD variants identified at week 52, but the reason for this viral rebound for the remaining subjects is unclear. When the HBV DNA levels of subjects with YMDD-positive HBV were examined, the DNA levels began to increase at week 48, which was later than the rebound seen in many subjects. In addition, only one-half of subjects with HBV DNA breakthrough had YMDD variant virus, so YMDD mutations do not explain the reemergence of HBV DNA for many study subjects. No testing for other mutations possibly conferring resistance was performed, so the development of other resistant mutants could have contributed to HBV DNA rebound. It is difficult to compare the HBV DNA results obtained in study NUC30903 with those seen in clinical trials of adults since different assays were used, but viral rebound was described in a substantial number of adult subjects as described in the original NDA review. While this viral rebound is concerning and the reasons for viral rebound should

be investigated, neither the significance of rebound or the benefits of a short term decrease in HBV DNA is known.

c. Effect of baseline variables and subgroup analyses on efficacy endpoints

Additional analyses were performed by the applicant and by FDA reviewers to examine the effect of baseline variables on outcome including baseline demographic characteristics and baseline HBV disease status. Subgroup analyses were performed for age, gender, ethnic origin, and country; other analyses were performed to determine the effect of baseline HBV disease on outcome as measured by baseline HBV DNA level, baseline ALT value, total Knodell score, and previous HBV treatment.

In logistic regression modeling and subgroup analyses performed by the applicant, subjects with higher ALT values at baseline, HBV DNA levels of less than 800 MEq/ml at baseline, higher Knodell scores at baseline were more likely to have a complete virologic response. As shown in Table 11, subjects with higher baseline ALT values were also more likely to experience seroconversion. Although these results suggest that there are subgroups of patients with chronic hepatitis B infection who would benefit more from treatment with lamivudine than other children, it is unclear which patients would benefit most from treatment with lamivudine. The results suggest that children with normal or low ALT values showed less benefit from treatment than other children. Children with lower HBV DNA levels had a greater likelihood of achieving CVR than those with higher HBV DNA levels regardless of treatment group. (Please see Table 4.3A in Dr. Hammerstrom's Statistical Review for subgroup analyses).

Subgroup analyses by subject age was performed by the applicant and the proportion of subjects with a complete virologic response by age group is shown in Table 12.

Table 12: Effect of Age on Proportion of Subjects with a Complete Virologic Response in NUC30903

Age (years)	Placebo	Lamivudine
2 – 6 yrs	3/38 (8%)	16/49 (33%)
7 – 12 yrs	5/31 (16%)	20/95 (21%)
13 – 17 yrs	4/26 (15%)	8/47 (17%)

Source: Study NUC30903, CSR, Volume 8.4, Table 17.

As shown in Table 12, treatment effect was greatest for the youngest children and decreased in the two older age groups. Because of this treatment difference by age noted for the primary efficacy endpoint, results of secondary efficacy endpoints were also examined for any evidence of differing response by age. As shown in Table 13, results for the ALT and HBV DNA response were similar for all age groups, and subjects in the lamivudine group, regardless of age, had a greater response to each secondary efficacy endpoint than did subjects in the placebo group.

Table 13: Response to Selected Secondary Endpoints at Week 52 by Age and Treatment Group in NUC30903

	ALT < ULN		Undetectable DNA		HBeAg Loss	
Age (yrs)	Placebo	Lamivudine	Placebo	Lamivudine	Placebo	Lamivudine
2 – 6	13%	57%	11%	59%	11%	38%
7 – 12	35%	68%	23%	69%	25%	25%
13 - 17	23%	66%	23%	55%	19%	21%

Source: see Dr. Hammerstrom's statistical review.

The applicant performed additional analyses in order to determine the reason for this treatment difference by age and concluded that it could not be fully explained. Although there were small differences in the baseline characteristics of HBV disease such as HBV DNA levels and ALT levels, these differences did not explain the differing results by age. FDA reviewers also examined CVR by weight in order to determine if dosing lamivudine as milligrams per kilogram in younger children resulted in an higher drug exposure and thus greater efficacy than dosing as 100 mg daily regardless of weight in the adolescent population. In this analysis, subjects were divided into those weighing less than 33 kg and those weighing over 33 kg, since children weighing less than 33 kg received lamivudine 3 mg/kg daily and children weighing more than 33 kg received 100 mg daily. Overall, 28% of children receiving lamivudine who weighed 33 kg or less had a complete virologic response while 19% of children in the lamivudine group who weighed more than 33 kg had a complete virologic response at week 52. However, 65% of children receiving lamivudine in either weight group demonstrated a sustained ALT response at week 52, and approximately the same proportion of children in both weight groups had undetectable HBV DNA levels at week 52.

It is concerning that a treatment effect was also noted by age in NUCB2020 with adolescents having a lesser treatment effect in that study. Certain characteristics of HBV disease at baseline may partially explain the difference, but the reason for this differential treatment response is not understood. However, neither NUCB2020 or NUC30903 was designed for subgroup analysis and both studies had a relatively small number of subjects in the older age group (12 adolescents participated in NUCB2020 while 30 adolescents received placebo and 55 received lamivudine in NUC30903). In addition, adolescents receiving lamivudine in NUC30903 did show a greater treatment effect for both the primary efficacy endpoints and secondary efficacy endpoints than adolescents in the placebo group.

Subgroup analyses were also performed for other demographic characteristics. Gender, race and country had statistically significant interactions with treatment response as measured by the proportion of subjects with a CVR. Twenty-six percent of females had a CVR compared to 22% of males; however, males receiving placebo had a higher treatment response than females (16% versus 12%), so there was a smaller treatment difference noted for males than for females. Similar results were seen for analyses based on race or country. Response rates were fairly similar between the treatment groups but there was a varying response for subjects receiving placebo. Therefore, there was a larger treatment effect seen for Asians than Whites and for Eastern Europeans than for

patients in North America. This variation in placebo response may have been due to small numbers in many of the placebo groups in a study that was not powered for such subgroup analysis. In addition, for each subgroup a greater proportion of subjects receiving lamivudine had a CVR than subjects receiving placebo. Please see Dr. Hammerstrom's statistical review for further discussion of subgroup analyses.

Many of the children enrolled in NUC30903 had received previous treatment for chronic hepatitis B infection including 136 who were treated with an interferon and eight who were previously treated with lamivudine. Of the 136 children who had previously been treated with an interferon, 96 received lamivudine and 40 received placebo in NUC30903. Twenty percent of previously treated children in the lamivudine group achieved a CVR compared to 12.5% in the placebo group, which was similar to the overall study results. (Please note that the data for this analysis were obtained from datasets submitted on June 6, 2001 and differ slightly from data provided on page 61 of the Clinical Study Report). Six children in the lamivudine group and two in the placebo group had prior treatment with lamivudine before entering this study. Although only one of these children had YMDD-positive HBV detected at week 52, none of the eight achieved a CVR; all eight had detectable HBV DNA levels and positive HBeAg at week 52. When these eight were excluded from the analysis of CVR, there was little change in the proportion of lamivudine subjects (24%) or placebo subjects (13%) achieving a CVR. Overall, previous treatment with an interferon appeared to have little effect on the treatment response to lamivudine, but children previously treated with lamivudine did not appear to benefit from further lamivudine treatment.

Overall, the use of lamivudine 3 mg/kg daily (maximum of 100 mg daily) over 52 weeks in children with chronic hepatitis B infection resulted in a treatment benefit as evidenced by the higher proportion of children with both loss of HBeAg and undetectable HBV DNA levels at week 52 of treatment. Sensitivity analyses of the primary efficacy endpoint raised some concern about the modest degree of treatment effect, however, there was a statistically significant treatment effect with the analyses which had been defined in the study protocol. In addition, the relationship of the primary efficacy endpoint (CVR) to other outcomes such as histopathologic changes and end-stage liver disease has not been established. Clinical trials of lamivudine in adult subjects have used liver histology as a surrogate marker with seroconversion, ALT changes, and changes in HBV DNA as secondary efficacy endpoints. The results for children in NUC30903 were similar to those noted in adult studies described in the original NDA review. Furthermore, the treatment benefit was further supported by the substantially higher number of lamivudine treated children with sustained ALT normalization and undetectable HBV DNA levels at week 52. Subjects with higher baseline ALT levels and higher baseline Knodell scores appeared to benefit more from the use of lamivudine suggesting that there are subgroups of children with chronic hepatitis B who will benefit more from treatment with lamivudine than others. However, at this time it is difficult to identify with confidence which subgroups of children should be treated There also appeared to be differences in treatment effect by age, gender, ethnic origin, and country. Although it was unclear how the varying response in placebo groups affected this result and why there was such a variation in placebo response, it is important to note that across

multiple subgroups and multiple outcomes, subjects who received lamivudine had a higher treatment response than subjects who received placebo. The effect of age on treatment effect is more concerning since similar results were noted in study NUC2020. However, regardless of age group, a greater number of subjects receiving lamivudine had a CVR than subjects receiving placebo and subjects receiving lamivudine had similar responses in the analyses of secondary efficacy endpoints. In addition, it is important to remember that this study was not powered to support such subgroup analyses.

8. FDA Analysis of Safety

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. The percentage of children who experienced a clinical adverse event was similar in the lamivudine and placebo groups, and clinical adverse events were generally signs, symptoms, and illnesses commonly seen in a pediatric population (i.e., cough, ENT infection, bronchitis). Ten serious adverse events were reported in seven patients, but none were considered to be drug related. Two subjects withdrew from the study. One of these was a patient in the lamivudine group with severe bruising and prolonged bleeding after a cut, and this adverse event may have been drug-related. However, there were no unexpected clinical adverse events and no clinical adverse events reported at an unusually high incidence.

Laboratory adverse events were uncommon and only one subject, a 16 year-old male receiving placebo, was withdrawn from the study due to a laboratory adverse event (increase in ALT to 1059 U/L). Grade 3 or 4 laboratory adverse events were reported in 13 (14%) placebo subjects and 18 (10%) lamivudine subjects, but except for Grade 3 or 4 elevations in ALT and in CPK, the number of subjects with any individual laboratory abnormality was low. Twenty subjects, seven in the placebo group and 13 in the lamivudine group reported Grade 3 elevations in ALT, and one placebo subject reported a Grade 4 increase in ALT. Fluctuations in ALT measurements were common for subjects in both treatment groups and are characteristic of chronic hepatitis B infection. Increased ALT values were usually isolated increases and measurements at the next visit were often much lower. It is of interest to note that ALT elevations occurred at any time during the study for placebo recipients but were usually seen early in the study for subjects receiving lamivudine. Eleven of the 13 subjects in the lamivudine with Grade 3 ALT elevations had the increased ALT measurement at either the week 4 or 8 study visit. In general, the ALT values were decreased and more consistent with baseline values by the next study visit. The reason for this increase in ALT early in the treatment of chronic hepatitis B is not clear, but it raises concerns of exacerbation of liver disease in response to treatment which subsequently subsides. Direct hepatotoxicity due to lamivudine was unlikely since the increase in ALT resolved quickly. These increases in ALT also did not appear to correlate temporarily with seroconversion. As shown in Table 8, elevations in ALT values were more commonly reported in younger children. In addition, Grade 3 and 4 increases in ALT were reported more common in women and in Asians regardless of treatment group. The reason for these differences is unclear but should be examined in future studies powered for subgroup analyses. Finally, post-treatment hepatic flares were

noted in studies of adults receiving lamivudine for chronic hepatitis B infection. However, post-treatment ALT values were not provided in the clinical study report for NUC30906. This analysis will be included in the discussion of the Safety Update Report.

Grade 3 and 4 elevations in CPK were reported more commonly in placebo recipients (five subjects) than in lamivudine recipients (two subjects). All increases in CPK resolved and no subjects were removed from the study because of an increased CPK. Only one subject, a lamivudine recipient with a Grade 2 increase in bilirubin at baseline, reported a Grade 3 or 4 elevation of bilirubin. No differences in albumin, white blood cell counts, hemoglobin, platelet count, or absolute neutrophil count were noted between treatment groups.

Overall, lamivudine was well tolerated with no unexpected clinical or laboratory adverse events reported. In addition, lamivudine is currently approved for use in children three months of age and older at a higher dose than that proposed for use in children with chronic hepatitis B infection. Grade 3 and 4 increases in ALT were reported in 13 subjects receiving lamivudine; however, these increases were isolated occurrences and did not require stopping study treatment. Data was not available in the Clinical Study Report to determine if subjects treated with lamivudine had increases in ALT after stopping lamivudine, so the safety analysis must be completed after review of the Safety Update Report.

9. FDA Analysis of HBV YMDD Genotypic Results

HBV YMDD mutations were found in 18% (30/166) of subjects who received lamivudine for 52 weeks; fully variant HBV was isolated from 11 subjects and mixed populations of between 5% and 95% resistant virus were isolated from 19 subjects. This rate of YMDD resistant variants after 52 weeks of treatment is consistent with results from clinical trials of adults in which 16 to 32% of subjects developed resistant virus. When the baseline characteristics for subjects with YMDD-positive and YMDD-negative virus were compared, subjects who developed resistance were younger (median age of 7.0 versus 9.0 years) and smaller (median weight of 23.4 kg versus 35.75 kg). When the development of YMDD resistant virus was examined for each age group in NUC3090, YMDD-positive virus was isolated from 32% of children from 2 to 6 years of age, 15% of children from 6 to 12 years of age, and 10% of children 13 years or older. There were no appreciable differences in either gender or ethnic origin between the subjects with and without variant virus at week 52. When baseline HBV DNA levels, ALT values, bilirubin levels, and Knodell scores were compared between subjects who developed YMDD-positive virus and those who did not, the only difference noted was in baseline HBV DNA levels. Children who developed YMDD variants had a median baseline HBV DNA level of 1,626 MEq/ml compared to 777 MEq/ml for children with wild type virus isolated at week 52. Although it is not suprising that children with higher HBV DNA levels developed resistance during treatment, it is unclear why the younger and smaller children developed resistant virus. The applicant did not attempt to explain this finding, but future studies should be done to investigate populations at risk for the development of YMDD variant virus.

In their analyses of efficacy data, the applicant determined that children with YMDD variants "tended to maintain improvements" in sustained ALT response and suppression of HBV DNA, but had a lesser response in HBeAg loss. Efficacy results in subjects who were treated with lamivudine and developed resistant virus are compared with results from both subjects who received lamivudine but did not develop resistant virus and those treated with placebo in Table 14.

Table 14: Efficacy Results for Subjects with and without YMDD-Containing HBV Variants

Efficacy Result at 52 Weeks	Non-Variant HBV	Variant HBV	Placebo
Complete Virologic Response	40/136 (29%)	0/30	12/95 (13%)
Sustained ALT Response	78/129 (60%)	14/30 (47%)	11/88 (13%)
3 Component Seroconversion	39/136 (29%)	0/30	12/95 (13%)
2 Component Seroconversion	43/136 (32%)	1/30 (3%)	14/95 (15%)
HBeAg Loss	44/136 (32%)	1/30 (3%)	14/95 (15%)
Undetectable HBV DNA	94/136 (69%)	9/30 (30%)	15/95 (16%)
ALT <ULN	90/136 (70%)	14/30 (47%)	15/88 (17%)

Source: Study NUC30903, CSR, Volume 8.4, Tables 15, 19, 21, 25, 28, 35,40 and Pages 94-98.

As shown in Table 14, the efficacy results for subjects with YMDD-positive HBV are clearly inferior to those for subjects with wild type virus isolated at week 52. In addition, the response rates for the serologic endpoints in the subjects who received lamivudine but developed variant virus were actually lower than the response rates for subjects receiving placebo. Although the ALT and HBV DNA responses in subjects with resistant virus were intermediate between the responses in subjects with wild type virus and in subjects who received placebo, the ALT and HBV DNA values for subjects with YMDD variants did not begin to increase until week 48. Since data for the first 52 weeks only was provided in the clinical study report, it is not clear if the ALT values and HBV DNA levels continued to rise and reached similar values to those of placebo recipients. However, our analyses of the available data clearly showed that subjects with YMDD-positive virus had a decreased treatment effect and the results for this subgroup varied little from the results seen in the placebo group.

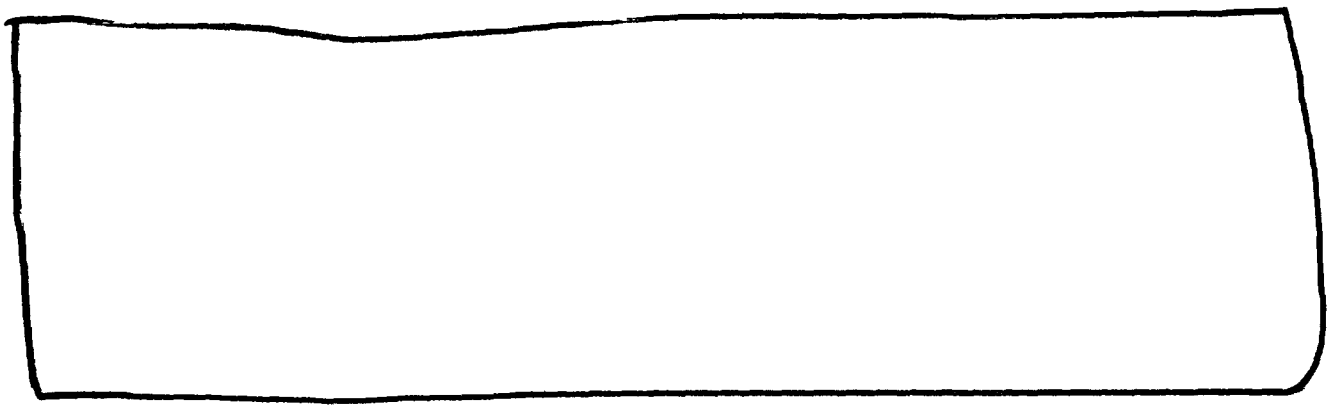
There was no difference in the overall incidence of adverse events in subjects with and subjects without YMDD-positive HBV isolated at week 52. More adverse events were judged to be drug-related in the YMDD variant group than in the group with wild type virus. There was a higher incidence of malaise and fatigue, headache, and nausea and vomiting in the YMDD-positive group than in the YMDD-negative group, but the significance of this finding is unclear and it might have been related to small patient numbers. There was no difference in the number of subjects with ALT elevations or in the number of subjects with Grade 3 and 4 laboratory abnormalities. Overall, there were no safety concerns in the review of subjects with YMDD variant HBV.

In summary, YMDD mutations were isolated at week 52 from 18% of subjects receiving lamivudine in study NUC30903. It is concerning that YMDD-positive virus was isolated more frequently in younger and smaller subjects, but the reason for this is unclear.

Median baseline HBV DNA levels were higher for subjects who had YMDD variant virus isolated at week 52. Subjects with YMDD positive virus had a lesser treatment effect than those with wild type virus isolated at week 52. However, it is unclear if there is any benefit from the short term suppression of HBV DNA levels and of ALT values in these subjects. No safety concerns in subjects with YMDD variants were raised in our review. Overall, our analyses suggest that there is a subgroup of patients at higher risk for the development of resistant virus, and that these subjects will benefit less from treatment with lamivudine.

10. Study Summary

Study NUC30903 was a double-blind, placebo controlled, multicenter trial evaluating the safety and efficacy of lamivudine in the treatment of chronic hepatitis B infection in children from two to 17 years of age. Two hundred eighty-eight children were randomized to receive either lamivudine (3 mg/kg once daily of the oral solution) or placebo in a 2:1 ratio. In the principal Phase III studies that formed the basis of approval for the treatment of chronic hepatitis B infection in adults changes in liver histopathology were used as the primary efficacy endpoint. It would be extremely difficult to obtain pre and post treatment biopsies in children; therefore, CVR at 52weeks was proposed as the primary efficacy endpoint prestudy and used by the applicant in NUC30903. The appropriateness of this endpoint for use as a surrogate marker in the treatment of chronic HBV infection is not known. Complete virologic response was seen in 23% of subjects receiving lamivudine compared to 13% of subjects receiving placebo (p=0.037). Because of concern about the suitability of the primary efficacy endpoint, the results for each secondary efficacy endpoint were examined carefully; and subjects in the lamivudine group had higher response rates than those in the placebo group for each of the secondary efficacy endpoints. There were concerns about a lesser treatment effect in certain study subgroups, particularly in adolescents, however, this study was not powered for subgroup analyses and subjects in each subgroup who received lamivudine had higher response rates than those receiving placebo. No safety concerns were raised on the review of this study, however, the review was limited by the lack of data past week 52. Finally, 18% of subjects who received lamivudine developed YMDD variant HBV at week 52. Although the efficacy of lamivudine was clearly decreased in these patients, no additional safety concerns were noted in patients infected with YMDD-positive HBV.



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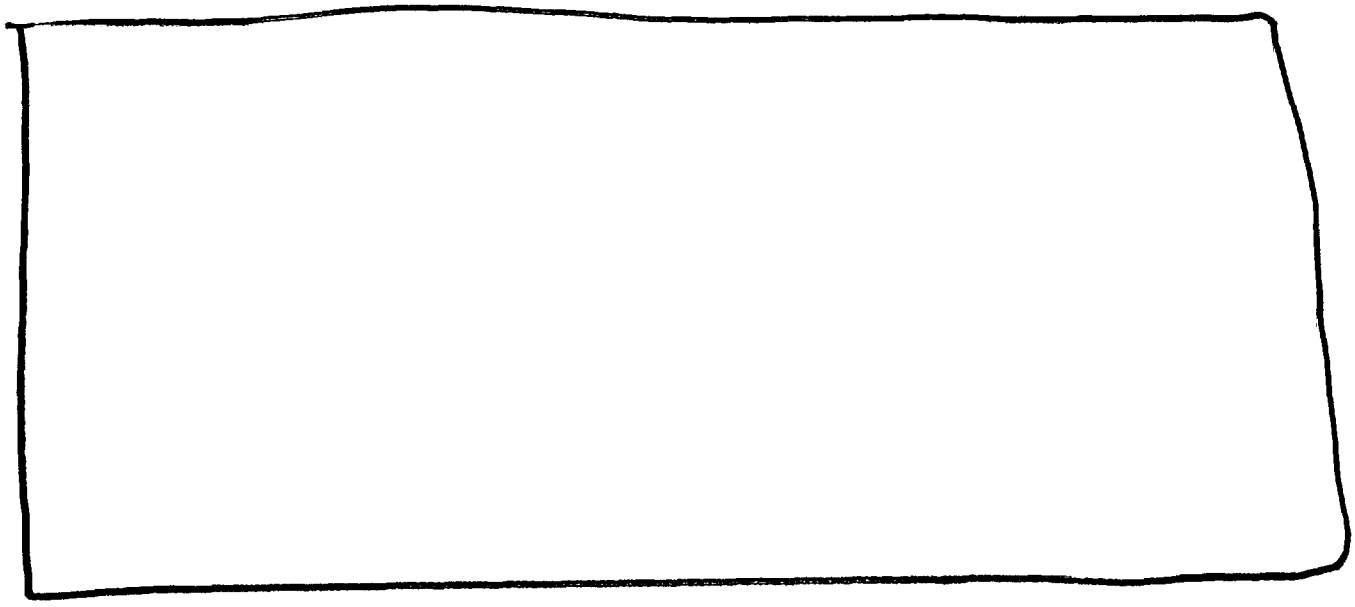
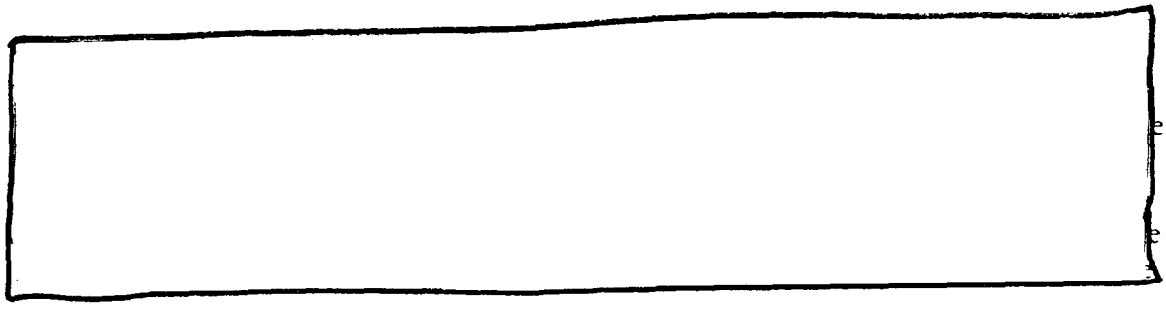


V. Financial Disclosure

Financial disclosure information was not provided for investigators in study NUCB2020 since this study had previously been submitted in June 1999. FDA regulations do not require the submission of financial disclosure information for studies that have been previously submitted.



VI. Labeling Issues

Labeling discussions were carried out through the review process. Preliminary DAVDP suggestions regarding the proposed draft labeling were provided to the applicant via telephone facsimile. Further revisions were carried out via telephone facsimile and teleconferences. Issues raised during labeling included the inclusion of selected secondary efficacy endpoints, results of subgroup analyses, and data concerning the decreased efficacy noted in subjects with YMDD variant HBV.

VII. Recommendation for Regulatory Action

The safety and efficacy of lamivudine 3 mg/kg daily to a maximum of 100 mg for 52 weeks in the treatment of chronic hepatitis B infection in children two to 17 years of age was supported by one large, Phase III pediatric clinical trial. Safety is further supported by the use of lamivudine 4 mg/kg twice daily in HIV-infected children. These findings

support the approval of lamivudine for the treatment of chronic HBV infection in children from two to 17 years of age.

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Medical Officer, DAVDP

Concurrences:
HFD-530/Division Dir/DBirnkrant /S/ 8/10/01
HFD-530/MOTL/Skukich
HFD-530/MO/Bstyrt

Cc:
HFD-530/NDA 21-003
HFD-530/NDA 21-004
HFD-530/Division File
HFD-530/Biopharm TL/KReynolds
HFD-530/Biopharm/JDiGiancinto
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