

group (2/22 versus 12/58). Caucasians were more likely to seroconvert than Orientals in the lamivudine monotherapy group (10/53 versus 1/16). ALT relapse in subjects with week 52 ALT responses was more frequent in the lamivudine monotherapy group (22/31, 71%) than the interferon group (4/11, 36%) or the combination group (4/18, 22%).

Table 19. Selected principal and subsidiary endpoints, NUCB3010

Outcome (wk 52)	Lamivudine	Interferon	Combination
HB e Ag seroconversion (CSR Table 16)	14/80 (18%)	12/64 (19%)	20/68 (29%)
HAI decrease \geq 2 points (CSR Table 24)	31/82 (38%)	25/69 (36%)	21/75 (28%)
Median decrease in HAI (CSR Table 32)	1 point	1 point	0
Fibrosis worsening on ranked assessment (CSR Table 31)	11/64 (17%)	16/54 (30%)	18/57 (32%)
Median percent HBV DNA reduction (maximum at any time point) (CSR Table 48)	98%	80%	98%
Sustained ALT normalization through to week 52 (CSR Table 52)	31/78 (40%)	11/66 (17%)	18/71 (25%)
HB s antigen loss at week 52 (CSR Table 39)	3/82 (4%)	3/69 (4%)	2/75 (3%)
Any HBV DNA below assay limit by week 52 (CSR Table 41)	71/80 (89%)	27/64 (42%)	62/69 (90%)
HBV DNA breakthrough by week 52 (CSR Table 44)	34/61 (56%)	7/17 (41%)	35/52 (67%)

III-D3. NUCB3010 Efficacy Results (FDA Comments)

Because there was no placebo arm in this study, only active treatments could be compared. Principal week 52 outcomes are summarized in Table 20.

Table 20. Principal endpoints, NUCB3010

Week 52 outcome	Histologic endpoint (n= 82 lamivudine, 69 interferon, 75 combination)	Seroconversion endpoint (n=80 lamivudine, 64 interferon, 68 combination)
Lamivudine successes	38%	12%
Interferon successes	37%	17%
Combination successes	29%	26%

Because of study size and low rates of seroconversion in all treatment arms, the confidence interval for the comparison between lamivudine monotherapy and interferon monotherapy does not exclude clinically meaningful differences between these two

treatment arms (favoring either therapy). For the histologic endpoint, the comparison between interferon and lamivudine also cannot exclude meaningful differences. Because there was no placebo arm, no conclusions can be reached about absolute treatment effect of either lamivudine or interferon monotherapy. The combination therapy arm showed an excess of week 52 seroconversion successes relative to lamivudine monotherapy and a histologic response rate that was numerically worse than the other arms; no evident advantage could be assumed for the combination, but inferiority was not proven, and no aggregate conclusion about combination therapy could be derived from considering these results together with those from NUCAB3011. In addition to the limited power to draw conclusions due to sample size, interpretation of this study (and of the combination therapy arm in NUCAB3011) is limited because of the study design. Interferon was started 8 weeks after lamivudine, all active treatment in the interferon-containing arms was stopped at week 24, and the primary comparison was on-treatment for lamivudine monotherapy and 26 weeks after the end of treatment for the other two arms: it is not clear that this design represents an appropriate comparison between treatment strategies. Some Advisory Committee consultants expressed concerns regarding the need for other ways of evaluating combination therapy with lamivudine and interferon (see section VII).

III-D4. NUCB3010 Safety Results (Summary of Applicant's Analysis)

No deaths were reported. Adverse events were reported for the majority of subjects in all treatment groups (at least 89% in each group). Groups receiving interferon had more reports than lamivudine monotherapy subjects for adverse events such as malaise and fatigue, temperature regulation disturbance, headache, nausea and vomiting, muscle pain, injection site reactions, arthralgia, feeding problems, weight problems, hair loss, decreased white blood cell count, neutropenia and quantitative platelet defects. Events such as dizziness, abnormal liver function tests, abdominal discomfort and pain, diarrhea, musculoskeletal pain, viral infection, and ear/nose/throat infections were relatively common without demonstrating major differences between groups.

It is stated that over 90% of interferon recipients experienced adverse events characterized as drug-related and that these were "typical of side effects associated with alpha-interferon administration" while 70% of subjects in the lamivudine monotherapy group had adverse events categorized as drug-related and these were "reflective of chronic hepatitis B disease." The most frequent drug-related adverse events in interferon recipients are listed as malaise and fatigue, headache, and temperature regulation; while frequent drug-related adverse events in the lamivudine monotherapy group are listed as malaise and fatigue, abnormal liver function tests, headache, and nausea and vomiting (section 9.3.1 of CSR). Serious adverse events were most common in the lamivudine monotherapy group (16 of 84 subjects), including six subjects with ALT elevations reported as serious adverse events (for four of these it was suggested that the ALT elevations were associated with seroconversion). Six subjects withdrew due to adverse events: one who became pregnant, two with adverse events in the combination arm (fever/chills/insomnia, headache/mental aberration), three with adverse events in the lamivudine monotherapy arm (two elevated CPK, one elevated transaminase levels).

III-D5. NUCB3010 Safety Results (FDA Comments)

There was no placebo group in this study and therefore no comparator group for lamivudine recipients except for patients who received interferon (and were known to have received interferon, as this treatment assignment was unblinded after week 8). As expected from other studies of interferon, there were numerous adverse events reported in the interferon groups. Many of the common events in these groups were consistent with the previously reported side effect profile of interferon therapy. In the lamivudine monotherapy group (which also was unblinded, by default, as subjects were known not to be receiving interferon), there were somewhat fewer adverse event reports overall but several subjects were withdrawn from the study due to adverse events including LFT and CPK elevations. In addition, in the serious adverse event narratives for follow-on study NUCB3017, it is noted that one patient (NUCB3017 patient number 28704) developed fulminant hepatitis after stopping lamivudine in NUCB3010 and during screening for the follow-on study; this patient also had a history of diabetes and biliary tract disease with gallbladder empyema, and the investigator considered both underlying disease and drug cessation as potentially related to the development of fulminant hepatitis. The combination group allowed only a partial evaluation of lamivudine-associated adverse events as lamivudine treatment in this group was shorter than for lamivudine monotherapy recipients.

Because grade 3 or 4 lipase elevations were more frequent in lamivudine than placebo recipients in NUCA3010 and NUCAB3011 and were not measured in NUCB3009, these results were reviewed for NUCB3010 although there was no placebo group for comparison. For the total study duration, grade 3 or 4 lipase elevations were reported for 7 of 83 lamivudine monotherapy recipients (8%), 5/70 interferon monotherapy recipients (7%), and 3/75 combination therapy recipients (4%).

CRFs were reviewed for subjects withdrawn because of adverse events. One subject in the lamivudine monotherapy group, withdrawn because of CPK elevations at week 12 and 16, was described as having had a previous event of CPK elevation during therapy with famciclovir, resulting in premature discontinuation after 12 weeks of famciclovir.

III-D6. Summary of Study NUCB3010

This study neither confirmed nor ruled out meaningful differences in principal outcomes among the treatment groups. In addition, the results do not resolve the question of whether this study design is appropriate for such comparisons. The adverse events observed in interferon-containing study arms were generally compatible with those which have been reported in other studies of interferon. Because there was no placebo control group, lamivudine monotherapy could not be compared against placebo for either safety or efficacy. Three subjects were withdrawn from the study because of adverse events associated with elevated liver function tests or CPK in the lamivudine monotherapy arm, and liver function test elevations were reported as serious adverse events with at least a

possible relationship to study drug in six lamivudine monotherapy recipients (four of these events reported as related to seroconversion).

IV. Brief Comments on Other Clinical Studies

A number of additional study reports were submitted in this NDA. Because the four principal phase III studies were the focus of the Advisory Committee presentations, efficacy considerations for approval, and labeling discussions, only brief summary comments will be included for the following studies.

IV-A. Clinical Study NUCB2020

Protocol NUCB2020 is a non-IND phase II study of lamivudine pharmacokinetics and short-term virologic marker responses in pediatric subjects with chronic hepatitis B virus infection. The CSR is in volumes 18-20 of NDA 21-003.

IVA1. NUCB2020 Study Design

A total of 53 children with chronic hepatitis B virus infection (with inclusion criteria of HB s Ag in serum for at least 6 months, HB e Ag and HBV DNA in serum at screening, ALT and AST below 300 IU/L) were enrolled in this study. Twelve adolescents (ages 13 through 17) were assigned to receive the adult dose of 100 mg/day lamivudine for 28 days. The younger subjects were randomized to receive doses of 0.35 mg/kg bid, 3 mg/kg daily, 1.5 mg/kg bid, or 4 mg/kg bid for 28 days. Measurements included serum lamivudine levels, HB e antigen, and HBV DNA (using a branched-chain DNA assay which differs in many respects from the solution hybridization assay used in the principal phase III studies).

IV-A2. NUCB2020 Efficacy Results (Summary of Applicant's Analysis)

The applicant proposed a dose of 3 mg/kg/day as providing the nearest approximation to drug exposure in adults receiving 100 mg/day. Loss of hepatitis e antigen occurred in one child in the 1.5 mg/kg bid group at week 12. HBV DNA measurements were performed using a branched-chain DNA assay and selected results are summarized in Table 21. A lesser response in the adolescent group in log₁₀ decrease in HBV DNA was noted by the applicant and potential reasons were considered (section 11 of study report) including less likelihood of supervision in this age group and lower baseline HBV DNA values allowing for lesser declines before reaching the assay limit.

Table 21. HBV DNA (branched chain DNA assay) changes in NUCB2020

Dose	0.35 mg/kg bid	3 mg/kg/d	1.5 mg/kg bid	4 mg/kg bid	100 mg/day (adolescents)
Week 4 Log ₁₀ decrease in HBV DNA (mean, median) (CSR Table 26)	2.6, 2.5	3.0, 3.0	3.1, 3.2	3.1, 3.2	2.3, 2.3
Number below assay limit at week 2 (CSR Table 19)	0/8	2/11	1/10	1/10	1/12
Number below assay limit at week 4 (CSR Table 19)	2/8	5/11	4/10	7/11	2/12
Number below assay limit at week 8 (CSR Table 19)	0/8	0/11	0/10	0/11	0/12

IV-A2. NUCB2020 Efficacy Results (FDA Comments)

Please see the Biopharmaceutics review for comments on the pharmacokinetic measurements. With respect to virologic results, interpretation is limited by the use of an HBV DNA assay which differs from that used in the principal phase III trials and for which no generally accepted standards for interconversion exist (and neither of which is FDA-approved), as well as by the short treatment period and the absence of supporting information for use of numerical changes in this HBV DNA measurement as indicators or predictors of clinical benefit. The difference in HBV DNA changes between the 13-17 year old group and the younger children is noted, and the possible explanations offered have been considered. If an inferior response is seen in the adolescent group because of limited supervision, the implications for clinical use might be of concern, because an adherence-related difference in treatment effect that is apparent during a one-month period under research conditions might be even more striking with much more prolonged treatment periods without the reinforcing context of a clinical trial. An attenuated response measured as log₁₀ change in viral load due to lower starting values (leading to a smaller change possible before values reached the assay limit) might be expected to be associated with more adolescent subjects falling below the assay limit during the one-month treatment than the younger children, but the opposite occurred. Overall, fewer than half the children in any dose group had HBV DNA values below the assay limit at the end of four weeks of treatment. The difference from results in adult studies may not be meaningful because of the different HBV DNA assays and cannot be taken to imply that children respond less well to lamivudine for chronic hepatitis B than adults; however, these results also are not proof that children do respond as well as adults.

IV-A4. NUCB2020 Safety Results (Summary of Applicant's Analysis)

Adverse events reported during this study included malaise and fatigue, cough, fever, diarrhea, headache, and viral respiratory infections.

IV-A5. NUCB2020 Safety Results (FDA Comments)

This study did not suggest salient differences in lamivudine adverse events between children and adults with chronic hepatitis B or between children with chronic hepatitis B and HIV-infected children. However, the small study size and limited treatment duration do not permit conclusions about long-term safety in children with chronic hepatitis B.

IV-A6. Summary of Study NUCB2020

This short-term pharmacokinetic study suggested that children may require a higher daily dose of lamivudine on a mg/kg basis to produce systemic drug exposure similar to that seen in adults at standard dosage. Because of the small size and short duration of the study, no conclusions can be drawn about clinical efficacy. Virologic effect cannot be compared to results in the available adult studies.

IV-B. Clinical Study NUCB3018

Protocol NUCB3018, "A follow-on study to determine the safety and efficacy of long-term lamivudine treatment in patients with chronic hepatitis B infection," is a non-IND follow-on study into which subjects from the Asian study NUCB3009 could be enrolled upon completing NUCB3009. A one-year interim report was submitted to _____ as one of the reports intended for inclusion in the new drug application.

IVB1. NUCB3018 Study Design

In the follow-on study NUCB3018, subjects who received placebo during NUCB3009 were switched to oral lamivudine 100 mg/day; subjects who received lamivudine 25 mg/day during NUCB3009 were re-randomized to oral lamivudine 25 mg/day or placebo in a 3:1 ratio; and subjects who received lamivudine 100 mg/day during NUCB3009 were re-randomized to oral lamivudine 100 mg/day or placebo in a 3:1 ratio. The study was planned such that subjects who remained on lamivudine for two years (one year in NUCB3009 and a second year in NUCB3018) would again be re-randomized to continued lamivudine or placebo, and so forth. Results from the first year of NUCB3018 are summarized in the NDA submission and the study is ongoing.

IV-B2. NUCB3018 Efficacy Results (Summary of Applicant's Analysis)

Of the 358 subjects in NUCB3009, 334 received rollover assignments in NUCB3018. Because the protocol allowed subjects with repeatedly elevated HBV DNA measurements

to receive open label lamivudine, treatment changed during the first year of NUCB3018 in a number of subjects, as summarized in the following table. The 25 mg lamivudine group will not be discussed except where specifically noted.

Table 25. Treatment assignments and open-label treatment, NUCB3018 (CSR section 8.2)

Year 1 assignment (3009)	Year 2 assignment (first year of 3018), n	Open-label during year 2 (n, %)
Lamivudine 25 mg	Placebo (n=31)	23 (74%)
Lamivudine 25 mg	Lamivudine 25 mg (n=101)	45 (45%)
Lamivudine 100 mg	Placebo (n=41)	37 (90%)
Lamivudine 100 mg	Lamivudine 100 mg (n=93)	26 (28%)
Placebo	Lamivudine 100 mg (n=68)	5 (7%)

Sustained HBV DNA response was defined as at least two consecutive measurements below the solution hybridization assay limit at least 7 days apart, with no two consecutive positives following, and with a value below the assay limit at week 104. Sustained response occurred in 37 (56%) of subjects receiving placebo followed by 100 mg lamivudine (PLA/LAM100), 2 (5%) of subjects receiving 100 mg lamivudine followed by placebo (LAM100/PLA), and 47 (52%) of subjects receiving lamivudine 100 mg followed by lamivudine 100 mg (LAM100/LAM100). Among subjects who switched to open label during year 2, sustained responses occurred in 3/5 PLA/LAM100 (60%), 21/37 LAM100/PLA (57%), and 3/26 LAM100/LAM100 (12%). In the group randomized to LAM25/PLA but switched to open label lamivudine 100 mg, 13/23 (57%) had sustained suppression; in the group randomized to LAM25/LAM25 but switched to open label lamivudine 100 mg, 15/45 (33%) had sustained suppression (CSR section 8.3.1).

HB e Ag seroconversion was reported at week 104 for 23% of LAM100/LAM100 and 2% of LAM100/PLA subjects. In the NUCB3018 CSR (section 8.4.1 and Table 24) it is stated that sustained HB e Ag seroconversion through to week 104 increased from 11% at week 52 to 18% at week 104 for LAM100/LAM100 subjects (by definition, the week 52 percentage should exclude subjects who met seroconversion criteria at week 52 and lost criteria for seroconversion between week 52 and week 104), and that "in a balanced randomisation one would expect the percentage of HB e Ag -ve/HB e Ab +ve patients re-randomised from lamivudine in year one to lamivudine or placebo in year two to be of the ratio 3:1. However, the re-randomisation at week 52 resulted in an uneven distribution of HB e Ag -ve/HB e Ab +ve patients in a ratio of 7:1 for lamivudine 100 mg (n=21) versus placebo (n=3)." Only 31 subjects had repeat liver biopsies (excluding open-label; CSR section 8.5.1); improvements were noted in subjects receiving lamivudine for two years, but expression of HB e Ag and HBV DNA in the liver were not notably reduced.

IV-B3. NUCB3018 Efficacy Results (FDA Comments)

HBV DNA above the solution-hybridization assay limit was more frequent in subjects who switched from lamivudine to placebo at 52 weeks than in those who continued lamivudine. However, a substantial proportion of those continuing lamivudine for a

second year (i.e. the first year of NUCB3018) also had re-appearance of HBV DNA leading to institution of open-label therapy, and this proportion was greater than in those receiving lamivudine for the first time in year 2 (the PLA/LAM100 group). Furthermore, the results for sustained response in open-label recipients suggest that subjects with HBV DNA re-emergence during the second year of active therapy were much less likely to experience subsequent sustained HBV DNA suppression with further treatment than were those who experienced HBV DNA re-emergence after stopping active therapy and were then re-treated; this finding in the applicant's analysis was supported by additional analyses of data derived from the line listings in the clinical study report (Appendix 15).

The HB e Ag seroconversion results, comparing LAM100/LAM100 against LAM100/PLA subjects at week 104, are difficult to interpret for several reasons. Overall numbers are small. The distribution of subjects meeting seroconversion criteria at week 52 was uneven in the secondary randomization (as also noted in NUCAB3011): thus, 20% of LAM100/LAM100 subjects and 7% of LAM100/PLA subjects met seroconversion criteria at week 52 when there was no treatment difference between the two groups, and this difference appears potentially to explain much of the difference reported at week 104. From the data listings in Appendix 15 of the clinical study report (later confirmed from a requested electronic dataset), the following results were derived. Of the 140 NUCB3009 LAM100 subjects who had baseline positive HB e Ag and HBV DNA, 90 were assigned to LAM100 for a second year in NUCB3018. Of these 90, 18 (20%) met three-component seroconversion criteria at week 52. Of these 18, three did not meet seroconversion criteria according to actual results obtained at week 104 and two had no data after week 72 but met criteria at that time; of those who did not meet seroconversion criteria at week 52, six did meet criteria at week 104 (one additional subject who met seroconversion criteria at week 104 was on open label therapy and would not have been counted as a success according to the applicant's analysis). Thus, the net gain in the LAM100/LAM100 group for seroconversion could be stated as 3% (18/90 to 21/90, 20% to 23%) using LOCF, 1% (18/90 to 19/90, 20% to 21%) if LOCF was not used and missing values were counted as failures, or 2% (18/90 to 20/90, 20% to 22%) if LOCF was not used but seroconverters were counted as successes after switching to open-label therapy. By any of these measurements the net gain from the second year of therapy appears to be small. Comparisons to the LAM100/PLA group confirmed that the proportion meeting seroconversion criteria at week 104 was greater in the LAM100/LAM100 group but that net changes between week 52 (when therapy was identical) and week 104 did not differ substantially between the two groups.

Histologic results were also difficult to interpret due to the very small number of biopsies. Ranked assessments of progression of fibrosis at week 104 were available for 7 subjects assigned to continue 100 mg lamivudine for a second year (Table 33 of CSR, which excludes open-label data): two (29%) were reported as worsened and one as improved.

IV-B4. NUCB3018 Safety Results (Summary of Applicant's Analysis)

Two deaths were reported, one from a road accident and the other from liver cancer diagnosed after a year of lamivudine 25 mg/day, 19 weeks of placebo, and two months of open-label lamivudine 100 mg/day (subject ID 03164). A second patient (03031), who received placebo during year 1 and was switched to lamivudine 100 mg/day, was reported to have liver cancer diagnosed after five and a half months on lamivudine. ALT elevations were reported with most pronounced values at week 64 (section 9.4.3) for subjects switching from lamivudine to placebo at week 52.

IV-B5. NUCB3018 Safety Results (FDA Comments)

An additional death occurring after the week 104 analysis was described in the Integrated Summary of Safety (p. 134; patient ID 2871). This report described a patient in Hong Kong who received placebo for the first year in NUCB3009 with worsening Knodell score, then switched to lamivudine 100 mg with a marked improvement in Knodell score (12 to 4) during the second year, and within the next several months on continued lamivudine had laboratory evidence of recrudescence of liver disease accompanied by detection of HBV YMDD and pre-core mutations, followed by "clear progression of liver disease with the development of ascites, jaundice, coagulopathy, and renal failure," and died apparently from complications of spontaneous bacterial peritonitis. Also, a 15-day report to NDA 20-564 (ID #B0059412) was received during the review process, which described a patient in Taiwan who developed hepatic decompensation and resistance during a follow-on study which appeared likely to be NUCB3018 from the description, and more information was requested from the applicant on October 22, 1998. A second report of hepatic decompensation in a follow-on study was subsequently received as a 15-day report. The applicant's analysis dated November 13, 1998 suggested that episodes of hepatic decompensation in two NUCB3018 patients (patient 3030, corresponding to MedWatch report ID #B0059412, and patient 3150) may have been associated with seroconversion episodes. These events in combination with those reported in NUCB3010 led to a request for additional surveillance for seroconversion-related hepatitis flares in lamivudine-treated patients in discussions of phase IV commitments.

IV-B6. Summary of Study NUCB3018

This interim summary of the first year of NUCB3018 (representing the second year of study because all subjects were previously enrolled in NUCB3009) provides some supporting evidence for the hypothesis that sustained suppression of HBV DNA (at least when measured by a relatively insensitive assay) is more frequent with more prolonged lamivudine treatment than with a one-year course followed by cessation of active treatment. However, even in subjects assigned to continue lamivudine, HBV DNA was detected by solution hybridization assay during the second year in a substantial proportion, and these patients were less likely to have sustained suppression with further treatment than either subjects starting lamivudine for the first time in NUCB3018 or subjects with positive HBV DNA after switching from lamivudine to placebo. The

seroconversion results and histologic results do not provide firm conclusions regarding added benefit from a second year of treatment. The safety results include illustrations of clinically significant progression of disease in association with emergence of resistance-related viral mutations even after prolonged treatment with apparent good initial response, and hepatic carcinoma diagnosed after some months of treatment; more information and longer follow-up is needed to determine the impact of lamivudine on overall rates of hepatic decompensation and hepatocellular carcinoma.

IV-C. Clinical Study NUCB3014

Protocol NUCB3014 is a non-IND study of subjects with chronic hepatitis B characterized by negative HB e antigen and positive HB e antibody with positive HBV DNA and elevated transaminase (presumed pre-core mutant virus). An interim report was submitted to _____ as one of the reports intended for inclusion in the new drug application.

IV-C1. NUCB3014 Study Design and Summary of Applicant's Analysis

A total of 125 subjects were randomized to receive placebo (n=65) or lamivudine 100 mg (n=60) daily. The HBV DNA assay used to determine eligibility was initially a solution hybridization assay and was changed in a protocol amendment to a branched-chain DNA assay. Subjects with HBV DNA below the branched-chain assay limit at 24 weeks were considered as responders. At 26 weeks, the blind was broken, nonresponders in both arms were dropped from the study (with an option to switch from placebo to open-label lamivudine in a separate protocol), and responders in the lamivudine arm were continued to a total of 52 weeks of treatment. Biopsies were performed at baseline and at one year in the lamivudine group (and "if clinically indicated" in the placebo group). The primary endpoint for analysis was defined as fall of HBV DNA below the assay limit plus normalization of ALT.

In each treatment group 54 subjects had elevated ALT and positive HBV DNA assay at baseline. Of these, 14 placebo and 49 lamivudine subjects had HBV DNA below the assay limit at week 24 and were therefore eligible to continue in the study (3 of the 14 placebo subjects and 34 of the 54 lamivudine subjects also had ALT normalization). At week 52, 7 placebo subjects and 39 lamivudine subjects had HBV DNA below the assay limit, of whom 5 placebo subjects and 35 lamivudine subjects also had ALT normalization (CSR Table 17). Histologic improvement (CSR Table 22), defined as at least 2 points' decrease in the Knodell score, was seen in 23/60 (38%) of lamivudine subjects (18 had missing data). Histologic information was available for only 3 placebo subjects, of whom one showed improvement and 2 worsened. In the placebo group, 51% of subjects had at least one HBV DNA value below the assay limit (CSR Table 38), compared to 100% of the lamivudine subjects. HBV DNA breakthrough was observed in 9/17 subjects with at least two consecutive values below the assay limit in the placebo group, and 15/54 subjects in the lamivudine group (CSR Table 40).

Emergence of YMDD mutations (Table 37 of Summary of Genotypic Resistance) in lamivudine-treated subjects was similar to reports from the principal phase III controlled studies (see section VI below): at week 26, 1 of 53 specimens (2%) showed a fully mutant genotype, and at week 52, 6 of 41 (15%) were mixed and 5 (12%) fully mutant for a total of 27% of specimens showing some evidence of YMDD mutations. However, in this study, YMDD mutations were also identified in a few subjects in the placebo group (1 of 53 mixed and 1 of 53 fully mutant at week 26; 1 of 16 mixed at week 52), while these mutations were only seen in lamivudine recipients in other studies; the report suggests that false positives, off-label contrary-to-protocol use of lamivudine, or rare spontaneous mutations might explain this finding.

IV-C2. NUCB3014 FDA Comments and Summary

On-treatment suppression of HBV DNA was common in the lamivudine group in this interim report, but is difficult to interpret without more information on the optimal endpoints for assessing clinical benefit in this patient group for whom the usual HB e Ag seroconversion measurements are not useful. Spontaneous suppression of HBV DNA at 24 weeks also was reported in 26% of placebo recipients. Because subjects with positive HBV DNA at 24 weeks were withdrawn and the blind was broken, this study is essentially uncontrolled after six months with respect to HBV DNA results, and is entirely uncontrolled with respect to histologic results (because placebo subjects were biopsied only "if clinically indicated," the 3 post-treatment biopsies in this group represent a highly selected subpopulation as well as being too small in number for useful comparisons). In addition to the pre-core mutations assumed to be present, YMDD mutations were observed in HBV from a few placebo subjects (in contrast to the principal phase III trials discussed in section VI; but note in NUCB3018 above that one patient with progression of liver disease in the presence of YMDD mutation during lamivudine treatment was also noted to have pre-core mutation in the same time period). Additional studies of genotypic mutations may help to define risk factors and patterns of occurrence.

IV-D. Clinical Study NUCA/B3016

IV-D1. NUCA/B3016: Study Design and Summary of Applicant's Analysis

An interim report is provided for this follow-on study into which subjects from several phase II and phase III studies could be enrolled for long-term epidemiologic follow-up off treatment to evaluate durability of seroconversion, with provisions for re-treatment if there was evidence of hepatitis B reactivation. Subjects who had completed NUCA3010, NUCB3010, or NUCAB3011 were eligible for entry into Stratum A of NUCA/B3016 if they had negative HB e Ag and positive HB e Ab on the last two measurements from the prior trial or negative HB e Ag without persistently elevated HBV DNA during at least 3 months off lamivudine treatment. The interim report included in the NDA noted a total of 55 patients entered into stratum A, 35 of whom (32 from the principal phase III studies

and 3 from a phase II study) had received lamivudine 100 mg daily as their prior-study therapy (CSR Table 2). Of the 35 prior lamivudine 100 mg monotherapy recipients in stratum A, 34 had negative HB e Ag and positive HB e Ab at entry into NUCA/B3016 (CSR Table 7), and 31 of these maintained negative HB e Ag and positive HB e Ab (with use of LOCF conventions and median follow-up of six months) through their last scheduled visit in the time period covered by the interim report (CSR p. 11, NDA volume 25 p. 26), and 2 were HB e Ag positive at last scheduled visit.

IV-D2. NUCA/B3016: FDA Comments and Summary

At least short-term durability of some seroconversion components was required for enrollment in this study; most patients enrolled after meeting these criteria did not show reversion to positive HB e Ag or negative HB e Ag during the short additional follow-up available in this interim report. Longer follow-up will be useful to better define durability of serologic responses.

IV-E. Clinical Study NUCA/B3017

IV-E1. NUCA/B3017: Study Design and Summary of Applicant's Analysis

This is a long-term follow-on study providing continued lamivudine therapy to subjects who did not experience HB e Ag seroconversion in certain phase II and phase III studies. An interim report is provided. Subjects who had completed NUCA3010, NUCB3010, or NUCAB3011 were eligible for entry into Stratum A of NUCA/B3017 if they had positive HB e Ag or negative HB e Ab, and either had positive HBV DNA or were within 2 weeks of their last dose of study drug in the previous trial. Only stratum A interim efficacy results (median follow-up of six months, using LOCF for HB e Ag and HB e Ab) are presented, indicating three-component seroconversion in 7% of patients (18 out of 249 with baseline positive HB e Ag and HBV DNA) and HB e Ag loss at last study visit in 15% (CSR pages 10-12, NDA volume 28 pages 14-16).

IV-E2. 3017: FDA Comments and Summary

In adverse event narratives, it is noted that one patient enrolled in this study (number 28704: CSR page 32, NDA volume 28 page 36) developed fulminant hepatitis during the screening period after stopping lamivudine in the pre-rollover study (see comments on NUCB3010 above). Another patient (number 28322: CSR page 30, NDA volume 28 page 34) previously enrolled in phase III study NUCAB3011 was withdrawn because of elevated transaminases and bilirubin: it was noted that "The investigator considered the raised ALT, AST, and hyperbilirubinemia to be possibly related to either a hepatitis flare (at sero-conversion) or possibly the study medication." Seroconversion details for this patient were not identified in either the CSR or the CRF. Longer follow-up is to be encouraged to help characterize both late treatment responses and long-term toxicities of lamivudine in this setting.

IV-F. Other Studies Including Open-Label and Compassionate Use

Open-label studies, phase II studies, and other studies were not used for efficacy evaluations because of factors such as lack of controls, small numbers, and/or short treatment duration. Serious adverse event (SAE) narratives were reviewed to complement the safety information derived from the principal phase III studies. Because these SAE narratives are dominated by over two thousand patients who have received open-label lamivudine for chronic hepatitis B, many of them having advanced disease and receiving drug on a compassionate use basis, a substantial number of SAEs would be expected as complications of underlying disease. Among the events reported were several occurrences of elevated pancreatic enzymes and/or clinical pancreatitis, several occurrences of hepatic decompensation following treatment cessation in which a possible connection to drug withdrawal was noted (and a few fatal outcomes), several deaths in the presence of viral mutations specified as YMDD mutations either in the Summary of Genotypic Resistance or in teleconference discussion with the sponsor (two from open-label compassionate-use study NUCB2014 and one from Japanese study LB-03; in addition to the NUCB3018 patient already noted), several reports of neutropenia, several reports of depression (some apparently pre-existing), several reports of hemorrhagic complications, and several reports of elevated CPK and/or muscle symptoms. One patient in Japanese study LB-03 had a liver neoplasm detected by ultrasound approximately eight weeks after completing a year of lamivudine treatment, subsequently diagnosed as hepatocellular carcinoma (see Safety Update section below for comments). No judgment of causality can be made for the vast majority of these reports because most of the events are compatible with known complications of advanced liver disease; however, particularly where the patterns overlap with events previously reported with lamivudine or where the reported events are complications of liver disease that treatment is designed to prevent, these reports were considered potentially useful for consideration in labeling and in design of postmarketing activities.

V. Safety Update

The safety update, dated July 29, 1998, provided additional information about adverse events in several open-label and follow-on studies. Of note in review of the safety update were an excess of lipase elevations in prior lamivudine recipients in NUCB3017 (grade 3 or 4 elevations in 10/147 or 7% of prior lamivudine 100 mg/day recipients versus 2/173 or 1% of prior recipients of "other", Table 5.12 of report). There were several reports in the safety update of hepatic malignancies diagnosed or suspected in patients who had received a year or more of lamivudine in open-label compassionate-use study NUCB2014. These reports illustrate the need for longer periods of study to determine whether lamivudine is useful in prevention of this outcome in such high-risk patients.

VI. Summary Comments and Exploratory Analyses

In considering approval and labeling issues and framing questions to the Advisory Committee, the principal studies were considered as a group, and exploratory analyses were performed to pursue some of the questions raised by the primary efficacy results. This section contains comments related to combined and exploratory analyses and to additional issues raised by the NDA contents such as emergence of resistance-related viral mutations and questions of efficacy and safety in special populations.

VI-A. Efficacy analyses

VI-A1. Principal endpoints

In all four principal Phase III clinical trials, data were collected which permitted analysis of both histologic and seroconversion outcomes. In the review process, controversy about the meaning of the total Knodell score was acknowledged, histologic outcomes were discussed by consultants both at the Advisory Committee meeting and in FDA internal consultations, and individual components of the Knodell score and other histologic and nonhistologic endpoints were taken into account as supporting information. Individual components of the principal seroconversion endpoint were examined in some subsidiary analyses; as noted in prior comments, the research solution-hybridization assay for HBV DNA used in these studies is one of a number of HBV DNA assays in current use which have quite different methodologies and sensitivities, different assays produce results which cannot be translated readily from one assay to another either with regard to absolute HBV DNA measurements or with regard to prognostic meaning, and there is limited information on the significance of specific numerical values. Therefore, these assay results are used only for exploratory comparisons within this group of studies and not as definitive endpoints in themselves.

All three placebo-controlled studies had significantly greater proportions of subjects with histologic improvement in the lamivudine 100 mg/day group than in the placebo group. The treatment effect was similar in magnitude across the three studies. The applicant's submission also included subsidiary analyses of ranked assessments of progression of fibrosis which indicated progression in a larger proportion of placebo recipients than lamivudine recipients in the U.S. study NUCA3010 and the Asian study NUCB3009 (but no meaningful difference in the interferon-nonresponders study NUCAB3011). In FDA review of these results, interpretations were sensitive to the treatment of missing data and to the measure of fibrosis, assessments of which studies showed an effect varied according to these sensitivity analyses, and the overall proportion of subjects showing progression in the one-year period of study was relatively small. Therefore, although there is the possibility of an effect, conclusions about its frequency and magnitude must await the availability of more definitive data.

In general, success rates for the principal seroconversion endpoint were lower than for the principal histologic endpoint, for both lamivudine and placebo subjects. In the Asian

study (NUCB3009), patients with seroconversion at week 52 were significantly more frequent in the lamivudine group than in the placebo group. In the U.S. study (NUCA3010), the number of missing values was large enough relative to the number of responders that statistical significance of the seroconversion comparison would be affected by any treatment-related imbalance in actual outcomes of subjects with missing values. However, overall the U.S. study yielded very similar results to the Asian study for both histologic and seroconversion outcomes at week 52. In the interferon-nonresponders study (NUCAB3011), there was not a significant difference in seroconversion outcomes at week 52 between lamivudine and placebo arms.

In the active-control study (NUCB3010), interferon monotherapy and lamivudine monotherapy had similar response rates but the power of the study was not adequate to rule out a meaningful difference favoring either treatment. Interpretation of this study was complicated by the timing of the histologic endpoint assessment; examination of the time course of seroconversions did not indicate whether a different timing of comparisons might have been more informative. The groups receiving lamivudine/interferon combination therapy in NUCB3010 and NUCAB3011 showed no clear-cut advantage over monotherapy in either study, but inconsistencies in the results between the two studies, together with uncertainty regarding the appropriateness of the comparison of different treatment durations and the most appropriate sequence of treatments for combination therapy, precluded any definitive conclusions about the combination.

VI-A2. Relationship between principal endpoints

Because serologic markers can be obtained more frequently and noninvasively than liver biopsies, it is of interest to examine whether seroconversion is a reliable indicator of histologic response in these studies. The correspondence between the two principal endpoints in individual patients was examined as described in the Statistical Review. In study NUCA3010, most week 52 seroconverters on lamivudine also showed histologic improvement, but absence of seroconversion did not show a strong relationship to histologic status. In the placebo group, no strong relationship between week 52 seroconversion status and histologic improvement was documented, but interpretation was difficult because of the small number of seroconverters. Analysis of the other placebo-controlled studies yielded similar conclusions.

VI-A3. Persistence of seroconversion and its components

There were two placebo-controlled studies with post-treatment follow-up periods of 16 weeks (U.S. study NUCA3010 and interferon-nonresponders study NUCAB3011). Differences between end-of-treatment and post-treatment seroconversion outcomes are discussed in the sections addressing these two studies above, as well as in the description of Asian follow-on study NUCB3018. Overall, the total number of subjects meeting seroconversion criteria was not large enough for clear conclusions about persistence or loss of treatment effect after the end of therapy, but it was evident that some subjects

gained or lost elements of the seroconversion definition either during or after treatment. Of subjects in the four principal phase III studies who had at least one negative HB e Ag value, 37% had at least one subsequent positive; of subjects who had at least one positive HB e Ab value, 39% had at least one subsequent negative. HBV DNA showed a markedly different time course from the composite seroconversion endpoint: the vast majority of subjects receiving lamivudine 100 mg/day demonstrated a fall in HBV DNA to below the limits of the assay employed, but subsequent re-emergence of HBV DNA was observed both on treatment and after the end of treatment, as illustrated in the applicant's analysis of HBV DNA breakthrough and HBV DNA relapse for each study.

Tables 23 and 24 show the proportion of observations below the assay limit at each time point for the lamivudine 100 mg/day and placebo groups on a by-study basis. In all 4 studies, the proportion of lamivudine subjects with HBV DNA below the assay limit peaked in the first 6 months of treatment. In three of the four studies, there was a subsequent steady decline in proportion below the assay limit, which began before the end of treatment. In the placebo groups for all three placebo-controlled studies, there was a gradual increase in the proportion of observations below the assay limit over time. In the calculations for these tables, missing values were excluded from the denominator in order to avoid an exaggerated decline attributable to loss to follow-up at later time points. The same tables with missing values included in the denominator as failures would lead to similar conclusions. Values are from the statistical analysis of the electronic datasets.

Table 23. Percent of HBV DNA values below assay limit (lamivudine 100 mg/day, 52 weeks)

Week	NUCA3010 (U.S.)	NUCB3010 (active-control)	NUCAB3011 (IFN non-resp.)	NUCB3009 (Asian)
0	5	2	8	2
2	52	—	—	46
4	69	—	—	66
8	74	74	80	74
12	73	—	—	73
16	79	72	83	—
20	85	—	—	—
24	76	65	84	67
28	76	70	78	—
32	67	—	*	—
36	70	65	76	66
40	67	—	*	—
44	67	55	67	—
48	56	—	—	—
52	62	61	65	72
56	46	35	*	—
60	34	38	*	—
64	30	32	*	—
68	35	—	*	—

*For NUCAB3011, weeks 32 and 40 not included because only one group of sites collected data; subgroup re-randomized to continued lamivudine had 63% below assay limit at week 52, 55% at week 56, 60% at week 60, 51% at week 64, 51% at week 68; subgroup re-randomized to stop lamivudine at week 52 had 68% below assay limit at week 52, 53% at week 56, 42% at week 60, 42% at week 64, 38% at week 68

Table 24. Percent of HBV-DNA values below assay limit (placebo)

Week	NUCA3010 (U.S.)	NUCAB3011 (IFN non-rasp.)	NUCB3009 (Asian)
0	3	4	3
2	6	—	1
4	3	—	4
8	8	16	1
12	9	—	1
16	11	21	—
20	14	—	—
24	16	17	11
28	24	19	—
32	23	*	—
36	25	21	8
40	27	*	—
44	27	24	—
48	28	—	—
52	23	26	19
56	24	26	—
60	25	29	—
64	15	28	—
68	30	30	—

*For NUCA3011, weeks 32 and 40 not included because only one group of sites collected data

VI-B. Safety analyses

Because lamivudine is already a marketed drug for HIV therapy at a higher dose than that used in the phase III studies for hepatitis B, its clinical safety profile has been explored to a large extent in previous studies. In the studies of hepatitis B, the potential for emergence of viral resistance, re-emergence of HBV DNA during treatment, and post-treatment hepatitis flares appeared as issues with implications for both efficacy and safety over the long term. The following discussion will address endpoint events associated with re-appearance of HBV DNA during lamivudine therapy after initial suppression and emergence of the specified genotypic mutations associated with reduced HBV susceptibility to lamivudine (YMDD variants, designated as mixed or fully mutant genotypes) that were assayed in these studies. Several issues related to liver function will then be briefly addressed, as well as more general clinical and laboratory adverse events.

VI-B1. Endpoints associated with on-therapy HBV DNA re-emergence

The exploratory analysis of proportion of subjects with HBV DNA values below the assay limit over time suggested that there is a group of patients in whom HBV DNA falls below the assay limit soon after institution of lamivudine therapy but subsequently rises again during therapy. To determine whether these patients represent a population which derives a smaller benefit from treatment (or loses treatment benefit over time), it would be desirable to have information about events within the liver at more frequent intervals

and over a longer time period than is generally feasible. To explore this question within the constraints of the data available, endpoint comparisons were conducted for patient groups showing different patterns of HBV DNA suppression and re-emergence among those who received lamivudine 100 mg daily for one year.

Two different approaches were used for this exploratory analysis (see Statistical reviews). For the first approach, the subgroups for this exploratory analysis were defined as follows (also see Advisory Committee transcripts).

- Patients with persistent suppression of HBV DNA were those who had at least one HBV DNA value below the assay limit during the first 24 weeks of lamivudine treatment and had HBV DNA below the assay limit at week 52.
- Patients with early suppression followed by re-appearance had at least one value below the assay limit before week 24 of lamivudine treatment but were HBV DNA positive at week 52.
- Patients with late suppression had no values below the assay limit before week 24 of lamivudine treatment but were below the assay limit at week 52.
- Repeatedly unsuppressed patients were those who had no values below the assay limit before week 24 of lamivudine treatment and were HBV DNA positive at week 52.
- Combined results for subjects in placebo groups were used for an additional comparison.

The second approach, described in Dr. Soon's review, required repeated HBV DNA values below the assay limit for confirmed response and repeated values above the assay limit for definition of rebound (except for week 52 where a single value was sufficient). Each of these analyses suggested that patients who experienced re-emergence of HBV DNA during lamivudine treatment after an initial fall below the assay limit were less likely to have week 52 results showing histologic improvement, loss of HB e Ag, gain of HB e Ab, or normal ALT than patients who experienced HBV DNA fall below the assay limit which was durable during the 52 weeks of therapy.

VI-B2. Treatment-emergent genotypic mutations associated with reduced drug susceptibility

YMDD-region genotypic variants associated with lamivudine resistance have been observed in subjects with re-appearance of HBV DNA during lamivudine therapy. In the four principal phase III studies, YMDD-region genetic variants were not observed in placebo recipients, were infrequent in lamivudine recipients at 24 weeks, and were observed with increasing frequency in lamivudine recipients at week 52. The following table shows YMDD variants in lamivudine 100 mg/day monotherapy groups as a percentage of all samples with available results yielding a genotype or a report of no PCR-amplifiable HBV DNA (at week 52, or week 48 if week 52 was not available and week 48 was): these values will be referred to as one-year genotypes. Study NUCB3009 (the Asian study) showed a lower prevalence of YMDD variants than the other three studies, as well as a lower prevalence of fully mutant variants relative to mixed mutants (as noted above, this study was also the only one of the four that did not

appear to have a progressive decline in proportion of subjects below the solution hybridization assay limit on therapy). In the subset of patients from this study who had repeat genotyping after receiving lamivudine 100 mg/day for a second year in Study NUCB3018 (Tables 26 and 28 of Summary of Genotypic Resistance), the prevalence of YMDD mutations was 42% (of 74 specimens tested), and fully mutant variants represented 77% of all mutant-containing specimens. In liver transplant patients in NUCA3005, it is reported that YMDD mutations were detected in 27/42 (64%; 8 or 19% mixed, 19 or 45% fully mutant) of subjects with specimens examined after 52 weeks of lamivudine therapy (Summary of Genotypic Resistance Table 45). However, the proportion of subjects with YMDD mutations detected was not uniform in smaller studies of transplant patients (Tables 38-43 of Summary of Genotypic Resistance).

Table 25. Resistance-associated genotypes at one year by study (from Tables 11, 13, 16, and 22 in Summary of Genotypic Resistance)

Study	NUCB3009 (Asian)	NUCA3010 (U.S.)	NUCB3010 (active-control)	NUCAB3011 (IFN non-resp.)
Mutants (mixed or full) as % of total	16%	32%	31%	27%
Fully mutant isolates as % of all mutant specimens	33%	93%	58%	63%

% of total = % of all specimens for which a genotype or a result of no PCR-amplifiable HBV DNA was available.

VI-B3. Relationship of week 52 endpoints to resistance-associated genotypic mutants

The relationship of one-year genotype in patients receiving lamivudine 100 mg daily in the four principal phase III trials to week 52 endpoints was explored using methods similar to those described for the relationship of HBV DNA re-emergence to week 52 endpoints. Results were compatible with the applicant's analyses in Tables 50, 51, and 53 of the Summary of Genotypic Resistance in that lamivudine-treated subjects with mutant virus were less likely, when compared against lamivudine-treated subjects without evidence of YMDD mutations, to have histologic improvement, HB e Ag seroconversion components, or normal ALT. Subjects with mutant virus had greater likelihood than placebo subjects of week 52 histologic improvement and appeared much more similar to lamivudine-treated subjects without viral mutations for this endpoint; for the other endpoints examined, subjects with mutant virus appeared intermediate between lamivudine-treated subjects without viral mutations and placebo subjects, or closer to the placebo subjects. Because of the late appearance of mutants in most patients and the one-time histologic sampling, it was not possible to evaluate any histologic effects that might require longer time periods to appear. As YMDD mutants were often observed in patients who had HBV DNA above the solution-hybridization assay limit at week 52 of lamivudine, similarity of other week 52 outcome patterns between the subgroup of lamivudine-treatment patients defined by re-emergence of HBV DNA and the subgroup defined by detection of YMDD mutations was not unexpected.

The exploratory analyses in this and the preceding sections suggest that some subjects

with YMDD mutations and/or subjects with HBV DNA re-appearance may have diminished benefit from lamivudine at one year, and it is not possible to predict whether longer follow-up would show that these subgroups continue to have intermediate results or have outcomes converging with those of subjects receiving no active treatment. Therefore, additional information may be needed to permit conclusions about the risks and benefits of stopping or continuing treatment after emergence of viral resistance-related mutations and/or re-emergence of HBV DNA during lamivudine treatment.

VI-B4. Clinical adverse events and resistance-associated viral mutants

Clinical adverse events are difficult to identify in relation to viral genotype because they may overlap with expected consequences of underlying liver disease and evaluation may be subjective. In the narrative reports of serious adverse events from all clinical trials (including a large number of patients with late-stage liver disease at high risk for spontaneous complications), four deaths were described in association with YMDD mutant hepatitis B virus and progression of liver disease. Two of these were in liver transplant recipients receiving lamivudine under open-label compassionate-use protocols.

VI-B5. Exacerbations of liver function abnormalities

In addition to resistance issues, the major safety concern associated with lamivudine for hepatitis B has been the potential for exacerbations of liver dysfunction associated either with treatment (including hepatitis B flares associated with resistance or seroconversion, or direct hepatotoxicity of treatment) or with stopping treatment (post-therapy rebound). Such events may be particularly difficult to analyze because they overlap with the natural history of hepatitis B and might be affected either beneficially or detrimentally by treatment; therefore, like other events in the course of a disease characterized by spontaneous exacerbations and remissions, uncontrolled data must be interpreted with great caution and even controlled data may be subject to varying interpretations.

Transaminase elevations at week 52 in the presence of YMDD variants have been summarized above and were generally higher than in subjects with wildtype virus but no higher than in placebo recipients. Transaminase flares after cessation of therapy have been noted in lamivudine recipients in controlled studies and summarized in the comments on individual studies above. In open-label studies, there have been several reports of hepatic decompensation leading to death or liver transplant in which some of the component events were reported as at least possibly related to rebound or withdrawal of drug. Generally, these cases do not permit any definite assessment of causality.

Several adverse event reports of elevated liver function tests in lamivudine-treated subjects in NUCB3010 were identified by the applicant as occurring in association with seroconversion. Two reports of "severe hepatic decompensation" in the Asian follow-on study NUCB3018 were also described as temporally associated with seroconversion. There is insufficient information at this time to permit conclusions about the risk of seroconversion-associated hepatitis flares in lamivudine-treated patients, to compare this

risk with that associated with seroconversion in other settings (interferon treatment or spontaneous), or to evaluate potential clinical implications in patients with varying degrees of underlying decompensated liver disease.

VI-B6. Other clinical and laboratory events

Other adverse events have not shown any strikingly different patterns from those reported with the use of lamivudine for treatment of HIV infection. Grade 3 and 4 lipase and CPK elevations have been somewhat more frequent in lamivudine 100 mg/day treatment groups than in placebo groups in the studies for which those comparison could be made. Although these have not been associated with major clinical complications, review of case reports suggests that an association with drug is plausible in at least some cases, and the laboratory differences suggest that attention to possible muscle and pancreatic events may be warranted with greater long-term experience in a broader patient population.

VI-C. Special populations

VI-C1. Dual infection with HBV and HIV

In addition to emergence of HBV viral genotype variants, another resistance-related issue in the treatment of hepatitis B with lamivudine is the emergence of lamivudine-resistant HIV during lamivudine monotherapy. Because risk factors for HIV and HBV infection overlap, some patients started on treatment for hepatitis B might have undiagnosed or untreated concomitant HIV infection, and appropriate information for care providers and patients needs to be considered in order to minimize the risk of inadvertent monotherapy of HIV-infected persons that might jeopardize options for subsequent HIV therapy.

No studies of efficacy of lamivudine for treatment of chronic hepatitis B in patients dually infected with HIV and HBV were included in this NDA. Adverse events in dual HIV/HBV infection were examined in a retrospective analysis of hepatitis B surface antigen positive patients in the CAESAR trial of lamivudine in combination regimens for treatment of HIV infection. There was an excess of neutropenia reports in lamivudine-containing treatment arms (NDA Volume 32, CSR Table 11), including a few reports that were considered drug-related and/or serious or led to drug discontinuation, as well as a somewhat greater frequency of ALT shifts to grade 3 or 4 in the small number of subjects with grade 1 or 2 baseline elevations (CSR Table 16).

VI-C2. Children with chronic hepatitis B

There are a number of unanswered questions related to potential use of lamivudine for chronic hepatitis B in children. A short-term pharmacokinetic study in children provided limited safety information in chronic hepatitis B and included HBV DNA measurements using a different assay from that used in the principal phase III controlled studies in adults. These assays do not provide results that can readily be directly compared or

converted from one to another. The available results do not firmly establish that HBV DNA can be converted to below assay limits as rapidly or in as large a proportion of children and adolescents as has been observed in adult studies, and there has been no possibility to evaluate potential for seroconversion, histologic response, re-emergence of viral DNA on therapy, or development of resistance.

VI-C3. Advanced liver disease

There is limited information on the use of lamivudine in advanced liver disease. In compassionate-use studies, a wide range of serious adverse events has been reported (see section IV-F). In most such cases, there is no specific evidence that would permit evaluation of whether there is any causal relationship with lamivudine or whether the events were part of the natural history of underlying disease in these seriously ill patients.

VI-C4. Liver Transplant Patients

Lamivudine has been used in open-label studies in HBV-infected patients before and after liver transplant. From the information available thus far, it is difficult to draw conclusions about either efficacy or safety; such conclusions would be facilitated by controlled studies where these are ethical and feasible, and by rigorous placement of study results in historical context.

VI-C5. Patients with Pre-Core Mutant Virus

The limited information provided regarding use of lamivudine in patients with presumed pre-core mutant virus suggests that rapid decreases in HBV DNA can be achieved in many patients, but the usual seroconversion markers are not useful in this setting and no controlled histologic results are available. In this patient population, occasional detection of YMDD mutant HBV has been reported in patients not receiving lamivudine.

VI-C6. Persons at Risk of Hepatitis B Transmission

There is likely to be interest in the possibility of using lamivudine to reduce risks of person-to-person transmission of hepatitis B. No data exist to address this issue at present, and study of this possibility should not interfere with the use of available effective immunizations, but a future role could be considered for study of lamivudine as an adjunct in persons at risk of vaccine failure.

VII. Advisory Committee Discussion

These applications were presented to Antiviral Drug Advisory Committee members and consultants in an open session on October 6, 1998. The applicant's proposals were discussed by teleconference during preparations for the Advisory Committee meeting, including issues reflected in draft labeling and in draft materials for the Advisory Committee. Questions to the Committee included the following:

1. Does the information presented by the applicant support the safety and effectiveness of lamivudine for treatment of chronic hepatitis B?

a. If the answer is no, what additional studies are needed?

b. If the answer is yes, please address questions 2-6.

All voting members present voted yes on Question 1. Brief summaries of some of the discussion points related to questions 2-6 are given after each question below. Please see the meeting transcript for additional information.

2. What post-marketing information is desirable to determine optimal use in patients with compensated chronic hepatitis B disease (such as those included in the principal phase III trials), and in other populations such as pediatric patients or patients with decompensated liver disease? Discussants indicated that more information was needed to determine safety and efficacy of lamivudine in children. A need for information in pregnant women was also expressed. Discussants indicated that the effect of treatment could not be determined from present information in any populations other than those included in the principal phase III studies, and that more information would be needed and would be very desirable to demonstrate usefulness in patient groups such as those with decompensated liver disease, patients with liver transplants, and patients coinfecting with other viruses. A concern was expressed about potential consequences of post-treatment flares in patients with decompensated liver disease.

3. How should the following events influence decisions to stop or continue therapy: e antigen seroconversion, development of viral resistance, reappearance of viral DNA during therapy? How should patients be monitored for safety and effectiveness during and after therapy? How can the optimal treatment duration for specific patient groups be defined? Discussants expressed some doubt whether stopping treatment after e antigen seroconversion would be associated with predictably durable benefit. Discussants expressed concern about emergence of resistance and re-emergence of viral DNA on therapy, and the need for more study (including possible exploration of dose modifications as well as combination therapy) to define risk factors and find ways of minimizing these risks, but indicated that these events would not necessarily constitute a reason for stopping therapy. Need for more study to determine optimal monitoring and define appropriate treatment duration was acknowledged, and it was suggested that some patients might benefit from continuing therapy indefinitely but some patients might experience time-limited treatment benefits.

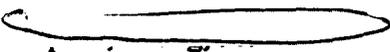
4. *Please discuss the implications of viral resistance development for long-term use of lamivudine monotherapy. What recommendations can be made for future development of combination therapy?* Discussants strongly supported studies of combination therapy, both to reduce development of resistance and to try to maximize likelihood of definitive responses to treatment. Some discussants indicated support for further studies of lamivudine in combination with interferon, suggesting that the design of the studies presented to them was not definitive for determining whether this combination would offer benefits greater than monotherapy; strong support for studies of combinations of antiviral drugs was generally expressed.

5. *To what extent can virologic and serologic results be used as a proxy for histologic changes? Please discuss the relationship between either virologic/serologic or histologic changes and long-term outcomes such as cirrhosis and hepatocellular carcinoma, and how such relationships can be confirmed.* Some disappointment was expressed at the capacity of virologic and serologic markers to indicate histologic status; a number of discussants expressed the opinion that histologic results would be necessary to show benefit in studies of new treatments, although biopsies would not be feasible in some settings and noninvasive markers might in many instances be used to follow individual patients in clinical practice. A need for better noninvasive markers of clinical response was expressed. Some discussants suggested that histology, despite its imperfections, is a reasonable indicator of progression to clinically important endpoints, but it was generally acknowledged that more long-term studies, and follow-up of subjects after completion of formal studies, are needed to delineate the relationships between study endpoints and decompensated cirrhosis or hepatocellular carcinoma.

6. *What information should be made available to physicians and patients concerning potential effects of lamivudine treatment for hepatitis B on unrecognized or untreated HIV infection? What are your recommendations regarding ascertainment of HIV status before treatment of hepatitis B with lamivudine, to avoid inadvertent use of a single nucleoside analogue in an HIV-positive patient?* Discussants indicated that HIV status should be determined before treatment of chronic hepatitis B with lamivudine to avoid inadvertent inappropriate monotherapy, as well as periodically during treatment so that intercurrent acquisition of HIV might be detected before development of resistance. A suggestion was made that patients and physicians should be made aware that if a patient is found to be dually infected with HBV and HIV, even a decision to institute lamivudine as part of a combination appropriate to HIV therapy would constitute a long-term commitment to combination HIV therapy which might not otherwise be chosen for all patients at the time infection is discovered.

VIII. Inspections

The Division of Scientific Investigations carried out inspections of sites in

 The DSI reviewer noted, "No objectionable

conditions were found which would impair the use of the data submitted in support of the pending NDA (See memo dated November 3, 1998)."

IX. Conclusions

Three placebo-controlled studies support the efficacy of lamivudine with respect to histologic improvement in patients with chronic hepatitis B. These studies were performed in adult patients with HB e Ag positive compensated chronic hepatitis B. Results using the three-component HB e Ag seroconversion endpoint also suggest an advantage of lamivudine over placebo although results were not uniform across studies. Data are not adequate to permit conclusions about comparison of lamivudine against interferon or combination treatments, efficacy in populations other than those included in the principal phase III studies, optimum duration of treatment and durability of response, or relationship between study endpoints and outcomes such as decompensated cirrhosis or hepatocellular carcinoma which might occur after decades of chronic infection.

The principal safety concerns have to do with exacerbations of liver disease that might be related to events such as emergence of viral mutations or rebound after stopping therapy. These require further exploration in phase IV, as they could alter the risk-benefit relationship in various settings in which this drug may be used. Other drug-related adverse events did not raise major new issues relative to experience already available with the approved use of lamivudine in combination treatments for HIV infection.

X. Labeling Discussions

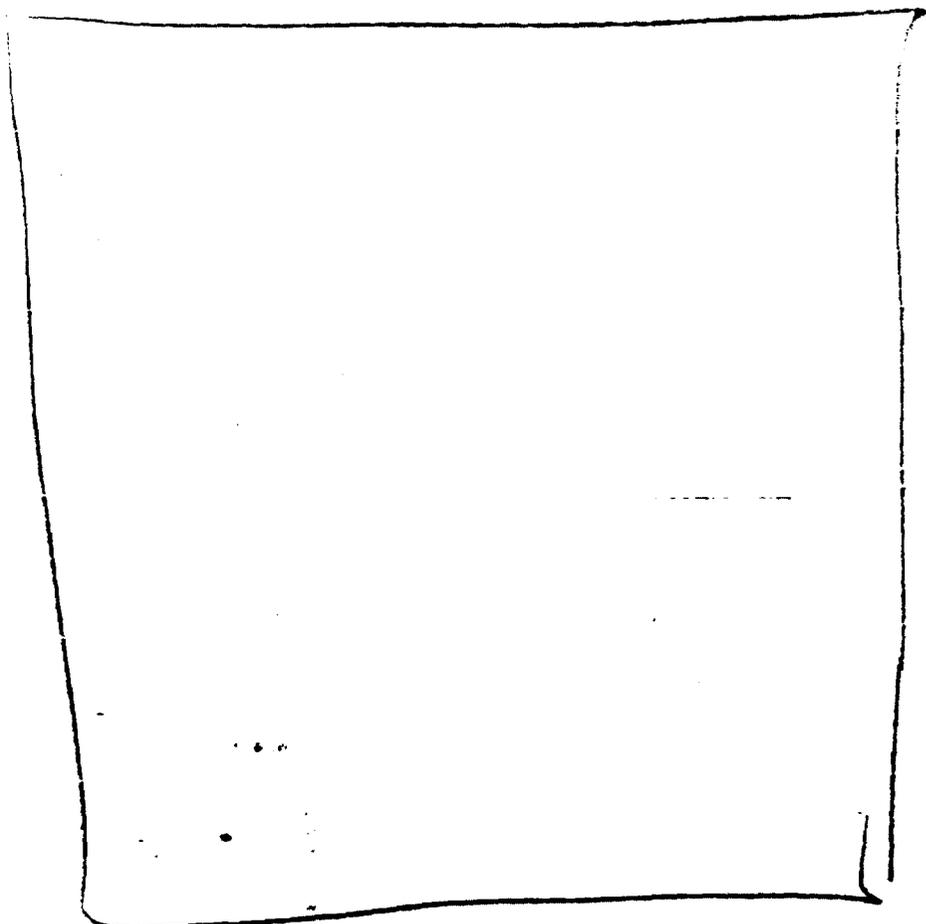
Labeling discussions were carried out throughout the review process. Preliminary DAVDP suggestions regarding the proposed draft labeling contained in the original NDA submission were provided to the applicant via telephone facsimile and were briefly discussed in the teleconference of September 17, 1998, which focused on the applicant's proposed draft slides for the Advisory Committee. Following the receipt of applicant's responses to the initial comments and consideration of the Advisory Committee discussions, further revisions were carried out via telephone facsimile and teleconferences. Topics of labeling discussions included the appropriate presentation in the package insert of issues such as uncertainties regarding duration of treatment and relationship between study endpoints and long-term outcomes, the lack of information regarding safety and efficacy in patient populations other than those included in the principal phase III studies, the potential for emergence of resistance and/or loss of treatment effect during therapy and for rebound after treatment cessation, and the need to consider HIV status as well as HBV diagnosis as a factor in treatment decisions.

XI. Recommendations

XI-A. Recommendations for Approval

Efficacy was demonstrated in three placebo-controlled studies showing a substantial and consistent treatment effect of lamivudine 100 mg/day for 52 weeks on the week 52 primary histologic endpoint. Two of the placebo-controlled studies also showed a treatment effect of lamivudine with regard to the composite seroconversion endpoint. These findings, together with the safety profile of lamivudine as outlined above, support the approval of lamivudine for the chronic hepatitis B indication described in the final package insert.

XI-B. Phase IV commitments



~~_____/S/~~
Barbara Styrt, M.D., M.P.H.
Medical Officer, HFD-530

Concurrence:

HFD-530/Dir/HJolson *HJolson 1/26/99*
HFD-530/MTL/SKukich *SK 12/28/98*

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HFD-530/NDA21003
HFD-530/NDA21004
HFD-530/NDA20564
HFD-530/NDA20596
HFD-530/Division File
HFD-530/Pharm/Verma
HFD-530/Micro/Iacono-Connors
HFD-530/Chem/Lunn
HFD-530/Stat/Soon
HFD-530/Stat/Levine
HFD-530/Biopharm/Rajagopalan
HFD-340
HFD-530/MO/BStyrt
HFD-530/MTL/SKukich
HFD-530/CSO/Zeccola

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