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**Application Number** 21-003  
21-004

**MEDICAL REVIEW(S)**

**Medical Officer's Review  
New Drug Application**

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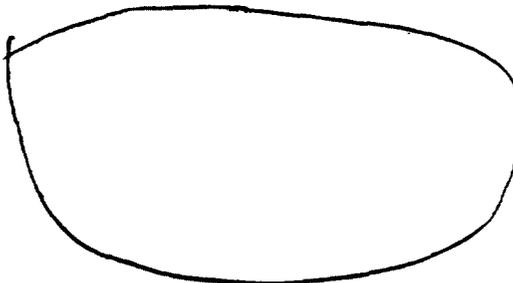
**Drug name:** Lamivudine (Epivir-HB, 3TC, GR109714X)

**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

**Related INDs and NDAs:**



**Related meeting minutes:** Pre-NDA meeting October 8, 1997  
Advisory Committee meeting October 6, 1998



TABLE OF CONTENTS

I. Resume	Page 6
II. Regulatory Background	Page 7
III. Four Principal Phase III Controlled Studies	Page 8
III-A. Clinical Study NUCA3010	Page 9
III-A1. NUCA3010 Study Design	Page 9
III-A2. NUCA3010 Efficacy Results (Summary of Applicant's Analysis)	Page 9
III-A3. NUCA3010 Efficacy Results (FDA Comments)	Page 11
III-A4. NUCA3010 Safety Results (Summary of Applicant's Analysis)	Page 12
III-A5. NUCA3010 Safety Results (FDA Comments)	Page 12
III-A6. Summary of Study NUCA3010	Page 13
III-B. Clinical Study NUCAB3011	Page 14
III-B1. NUCAB3011 Study Design	Page 14
III-B2. NUCAB3011 Efficacy Results (Summary of Applicant's Analysis)	Page 14
III-B3. NUCAB3011 Efficacy Results (FDA Comments)	Page 16
III-B4. NUCAB3011 Safety Results (Summary of Applicant's Analysis)	Page 18
III-B5. NUCAB3011 Safety Results (FDA Comments)	Page 19
III-B6. Summary of Study NUCAB3011	Page 20
III-C. Clinical Study NUCB3009	Page 20
III-C1. NUCB3009 Study Design	Page 20
III-C2. NUCB3009 Efficacy Results (Summary of Applicant's Analysis)	Page 20
III-C3. NUCB3009 Efficacy Results (FDA Comments)	Page 22
III-C4. NUCB3009 Safety Results (Summary of Applicant's Analysis)	Page 22
III-C5. NUCB3009 Safety Results (FDA Comments)	Page 22
III-C6. Summary of Study NUCB3009	Page 23
III-D. Clinical Study NUCB3010	Page 23
III-D1. NUCB3010 Study Design	Page 23
III-D2. NUCB3010 Efficacy Results (Summary of Applicant's Analysis)	Page 24
III-D3. NUCB3010 Efficacy Results (FDA Comments)	Page 25
III-D4. NUCB3010 Safety Results (Summary of Applicant's Analysis)	Page 26
III-D5. NUCB3010 Safety Results (FDA Comments)	Page 27
III-D6. Summary of Study NUCB3010	Page 27
IV. Brief Comments on Other Clinical Studies	Page 28
IV-A. Clinical Study NUCB2020	Page 28
IV-A1. NUCB2020 Study Design	Page 28
IV-A2. NUCB2020 Efficacy Results (Summary of Applicant's Analysis)	Page 28

IV-A3. NUCB2020 Efficacy Results (FDA Comments)	Page 29
IV-A4. NUCB2020 Safety Results (Summary of Applicant's Analysis)	Page 30
IV-A5. NUCB2020 Safety Results (FDA Comments)	Page 30
IV-A6. Summary of Study NUCB2020	Page 30
IV-B. Clinical Study NUCB3018	Page 30
IV-B1. NUCB3018 Study Design	Page 30
IV-B2. NUCB3018 Efficacy Results (Summary of Applicant's Analysis)	Page 30
IV-B3. NUCB3018 Efficacy Results (FDA Comments)	Page 31
IV-B4. NUCB3018 Safety Results (Summary of Applicant's Analysis)	Page 33
IV-B5. NUCB3018 Safety Results (FDA Comments)	Page 33
IV-B6. Summary of Study NUCB3018	Page 33
IV-C. Clinical Study NUCB3014	Page 34
IV-C1. NUCB3014 Study Design and Summary of Applicant's Analysis	Page 34
IV-C2. NUCB3014 FDA Comments	Page 35
IV-D. Clinical Study NUCAB3016	Page 35
IV-D1. NUCAB3016 Study Design and Summary of Applicant's Analysis	Page 35
IV-D2. NUCAB3016 FDA Comments	Page 36
IV-E. Clinical Study NUCAB3017	Page 36
IV-E1. NUCAB3017 Study Design and Summary of Applicant's Analysis	Page 36
IV-E2. NUCAB3017 FDA Comments	Page 36
IV-F. Other Studies Including Open-label and Compassionate Use	Page 37
V. Safety Update	Page 37
VI. Summary Comments on Clinical Studies and Exploratory Analyses	Page 38
VI-A. Efficacy Analyses	Page 38
VI-A1. Principal Endpoints	Page 38
VI-A2. Relationship Between Principal Endpoints	Page 39
VI-A3. Persistence of Seroconversion and Its Components	Page 39
VI-B. Safety Analyses	Page 41
VI-B1. Endpoints Associated with On-Therapy HBV DNA Re-Emergence	Page 41
VI-B2. Treatment-Emergent-Resistance-Associated Genotypic Mutations	Page 42
VI-B3. Relationship of Week 52 Endpoints to Genotype	Page 43
VI-B4. Clinical Adverse Events and Resistance-Related Viral Mutants	Page 44
VI-B5. Exacerbations of Liver Function Abnormalities	Page 44
VI-B6. Other Clinical and Laboratory Events	Page 45

VI-C. Special Populations	Page 45
VI-C1. Dual Infection with HBV and HIV	Page 45
VI-C2. Children with Chronic Hepatitis B	Page 45
VI-C3. Advanced Liver Disease	Page 46
VI-C4. Liver Transplant Patients	Page 46
VI-C5. Patients with Pre-Core Mutant Virus	Page 46
VI-C6. Persons at Risk of Hepatitis B Transmission	Page 46
VII. Advisory Committee Discussion	Page 47
VIII. Inspections	Page 48
IX. Conclusions	Page 49
X. Labeling Discussions	Page 49
XI. Recommendations	Page 50
XI-A. Recommendations Regarding Approval	Page 50
XI-B. Phase IV Commitments	Page 50
XII. Concurrences	Page 51

**APPEARS THIS WAY  
ON ORIGINAL**

## I. Resume

In support of safety and efficacy of lamivudine for treatment of chronic hepatitis B, the applicant has submitted the results of four adequate and well-controlled clinical trials with histologic and serologic endpoints at 52 weeks of therapy. The application provides additional safety data from interim reports of long-term follow-on studies and from open-label studies in patients with advanced liver disease. Limited pharmacokinetic and virologic information was submitted from a one-month dose-ranging study in children.

Three of the controlled trials provide comparisons of the dose of lamivudine proposed for marketing (100 mg daily) against placebo in patients with chronic hepatitis B accompanied by evidence of ongoing viral replication and liver inflammation but without evidence of hepatic decompensation. These three studies provide adequate evidence that lamivudine treatment results in improvement in the Knodell score (see criteria for liver biopsy improvement defined in section III) in a higher proportion of lamivudine recipients than placebo recipients. Two of the studies also show HB e antigen seroconversion (defined as loss of e antigen plus gain of e antibody plus decline in HBV DNA to below the assay limit for the solution-hybridization assay used in these studies) in a higher proportion of lamivudine than placebo recipients, while no significant difference in e antigen seroconversion was seen in the third study. The fourth study compared lamivudine 100 mg daily for 52 weeks against the previously FDA-approved regimen of interferon administered from week 8 to week 24; the study did not show a striking difference between these active-treatment regimens but did not provide enough information to exclude a meaningful treatment difference favoring either regimen. Similarly, treatment arms using a combination of lamivudine and interferon in two of the four studies did not provide enough information for adequate evaluation of this regimen.

In the placebo-controlled studies, normalization of ALT was more frequent in lamivudine than placebo recipients during therapy. Most lamivudine recipients (and a smaller proportion of placebo recipients) showed a decline in HBV DNA below the assay limit early in therapy, but on-treatment re-emergence of HBV DNA was noted in a substantial proportion of lamivudine recipients; increasing re-appearance of assay-positive HBV DNA was noted during off-treatment follow-up in subjects who stopped lamivudine and were followed for an additional 12 to 16 weeks. Emergence of HBV DNA genotypic mutations (YMDD mutations) associated with diminished *in vitro* lamivudine susceptibility was noted in 16% to 32% of subjects receiving lamivudine 100 mg daily for 52 weeks (but not in placebo recipients) in the four principal studies, and was associated with re-emergence of HBV DNA during therapy. Subjects with re-emergence of HBV DNA and/or emergence of YMDD mutations had evidence of diminished treatment response in comparison with lamivudine-treated subjects who did not have HBV DNA re-emergence or detection of viral mutations.

Frequencies of most clinical and laboratory adverse events were similar in lamivudine and placebo recipients. The most striking difference was the greater frequency of transaminase elevations in post-active-treatment follow-up in subjects who stopped

lamivudine at week 52 and had follow-up information collected after switching to placebo or no treatment, in comparison with subjects who received placebo through week 52 and were subsequently followed on placebo or no treatment. Grade 3 or 4 elevations of CPK and lipase were also more common in lamivudine than placebo recipients in studies which collected this information. In open-label and follow-on studies, reported adverse events included hepatic decompensation (including fatalities) in a few patients who had emergence of YMDD mutations during lamivudine therapy and in a few patients after stopping lamivudine therapy; assessments of causality were not possible in patients at high risk of hepatic adverse events due to their underlying disease, but information from these studies was used in discussions of label wording and phase IV commitments.

These applications were presented to the Antiviral Drug Advisory Committee on October 6, 1998, and there was a unanimous vote that the information presented by the applicant supported the safety and effectiveness of lamivudine for treatment of chronic hepatitis B. Issues raised in Advisory Committee discussions contributed to development of the package insert and phase IV commitments. Based on one-year histologic and serologic endpoints from placebo-controlled trials in patients with compensated chronic hepatitis B, these NDAs were approved on December 8, 1998.

## II. Regulatory Background

The initial IND \_\_\_\_\_ was submitted on \_\_\_\_\_ The adult phase I/II program was initiated in 1991 and the pediatric program in 1992. The focus of development for lamivudine in the treatment of HIV infection was shifted from monotherapy to combination therapy with zidovudine. Controlled trials in adults with surrogate marker endpoints for combination therapy were initiated in May 1993. A closed session meeting with the Antiviral Drugs Advisory Committee was held on January 11, 1995, to discuss NDA contents and design of clinical endpoint studies. The original NDA for lamivudine was submitted June 30, 1995, and received accelerated approval in the U.S. on November 17, 1995. The DSMB for NUCB3007 met on July 15, 1996, and recommended study termination. NUCB3007 was submitted as a supplemental NDA on November 26, 1996, and traditional approval was granted on April 11, 1997. Epivir® is indicated for use in combination with Retrovir® (zidovudine) for the treatment of HIV infection. A combination tablet containing lamivudine 150 mg and zidovudine 300 mg (Combivir™) was approved on September 26, 1997 for the treatment of HIV infection.

\_\_\_\_\_ for lamivudine for treatment of chronic hepatitis B was submitted October 23, 1992. Phase I and II trials and plans for phase III trials were discussed at a meeting between DAVDP and the sponsor on May 3, 1994. Development plans were discussed at a closed session of the Antivirals Advisory Committee on November 18, 1994. Protocols for two principal phase III studies under the IND were submitted in 1994 and 1995 (see descriptions in section III). A pre-NDA meeting was held October 8, 1997. Further

discussions of open issues were carried out by teleconference and telephone facsimile between the pre-NDA meeting and the submission of NDA 21-003 (lamivudine 100 mg tablets) on June 24, 1998, and NDA 21-004 (lamivudine 5 mg/ml oral solution) on June 29, 1998. These submissions were treated as new NDAs rather than efficacy supplements as an FDA decision: there were substantially new indications requested, and other major differences such as a different package insert and different proprietary name from Epivir®, lamivudine for treatment of HIV infection. There were 91 volumes in the NDA submission for 21-003 plus 130 volumes of study reports submitted to ~~\_\_\_\_\_~~ as reports intended for inclusion in the application for new drug approval for lamivudine for hepatitis B. NDA 21-004 was a 4-volume submission which included Chemistry, Manufacturing, and Controls information for the oral solution, with most information in other sections incorporated by reference to NDA 21-003.

Following the NDA submissions, a presentation of data was scheduled for an Antiviral Drug Advisory Committee meeting on October 6, 1998. Consultations were requested from the Division of Gastrointestinal and Coagulation Drug Products regarding evaluation of the histologic endpoint, and from the Center for Biologics Evaluation and Research regarding interferon-related elements of study design. The Advisory Committee discussion on October 6, 1998, and comments received from the Division of Gastrointestinal and Coagulation Drug Products and from the Center for Biologics Evaluation and Research in response to the consultation requests, provided some of the issues considered in labeling comments and requests for phase IV commitments.

### **III. Four Principal Phase III Controlled Studies**

The applicant has submitted four principal phase III controlled studies and most of the detailed review focuses on these studies (NUCA3010, NUCAB3011, NUCB3009, and NUCB3010). For phase III studies NUCA3010 and NUCAB3011 conducted under the IND using pre-reviewed protocols, the primary endpoint was histologic improvement on liver biopsy defined as at least 2 points decrease in the total Knodell score, and the principal secondary endpoint was three-component HB e antigen seroconversion defined as loss of e antigen plus gain of e antibody plus fall in HBV DNA to below the limit of the solution hybridization assay used in these studies, with principal analyses performed at week 52. For principal purposes of NDA review, these endpoints were treated as primary and co-primary respectively, and were considered applicable to all four principal studies (although multiple other subsidiary endpoints were measured in various studies, and the descriptions of specified studies note other endpoints that were originally proposed as primary in non-IND studies). Study reports were provided for an additional five studies designated by the applicant as phase III (most of these were interim reports of ongoing studies) plus a number of phase II studies: brief comments on these will be included where appropriate, but they were not part of the core basis for approval and have been treated as ancillary or supporting information. Data analyses from the applicant's submitted electronic datasets were provided by Biometrics reviewers Dr. Greg Soon and

Dr. Jonathan Levine and will be referred to in the descriptions of FDA analyses and comments; please see also the Statistical Review of these submissions. Information on emergence of HBV mutations associated with diminished *in vitro* susceptibility to lamivudine was provided for the four principal phase III studies (as well as other studies) in a separate section of the NDA (Summary of Genotypic Resistance). Datasets for this aspect of the clinical trials were requested from the applicant, and review comments are included in section VI below (Summary Comments and Exploratory Analyses).

### **III-A. Clinical Study NUCA3010**

Protocol NUCA3010, "A study of lamivudine or placebo in patients with chronic hepatitis B infection who are treatment naïve," was filed to ~~serial no. 100~~, March 1, 1995. The Clinical Study Report (CSR) was submitted ~~serial no. 321~~.

#### **III-A1. NUCA3010 Study Design**

NUCA3010 enrolled 143 patients at 34 centers in the United States, randomized 1:1 to receive lamivudine 100 mg/day or placebo for 52 weeks followed by 16 weeks of off-treatment follow-up, with primary analysis at the end of therapy. The primary endpoint was histologic response (improvement of at least 2 points in Knodell histologic activity index); secondary endpoints included serologic and virologic markers, additional histologic analyses, and transaminase normalization.

#### **III-A2. NUCA3010 Efficacy Results (Summary of Applicant's Analysis)**

Analyses are summarized from sections 7 and 8 of the CSR and accompanying tables. Patients ranged from 18 to 73 years of age and were classified as 83% male, 58% Caucasian/White, 17% Negroid/Black, 20% Oriental, 3% Hispanic, and 2% "other" (categories are discussed under NUCA3011). There were no major imbalances between groups in these characteristics. Route of hepatitis B acquisition included sexual contact (32%), vertical/perinatal (15%), intravenous drug use or transfusion (7%), and unknown (33%). The lamivudine group had 15 patients (23%) who reported vertical/perinatal acquisition as compared with six (8%) in the placebo group. The primary endpoint was reached by 52% of lamivudine patients and 23% of placebo patients ( $p < .001$ ). Responses did not differ notably by age or gender categories or between subgroups designated as Oriental, Caucasian, and "other", but in the subgroup designated as Black, no treatment effect was documented (responders 3/10 or 30% on lamivudine, 5/13 or 38% on placebo, section 8.3). Table 1 summarizes results for selected principal and subsidiary endpoints. Throughout the review, "CSR Table [number]" identifies a table in a Clinical Study Report used as a data source.

Table 1. Selected principal and subsidiary endpoints, study NUCA3010

Treatment	Lamivudine	Placebo
HAI decrease $\geq$ 2 points (CSR Table 18)	34/66 (52%)	16/71 (23%)
Necroinflammatory changes improved (ranked response) (CSR Table 19)	42/66 (64%)	24/71 (34%)
Fibrosis worsened (ranked response) (CSR Table 19)	3/66 (5%)	14/71 (20%)
Three-component seroconversion (week 52) (CSR Table 25)	11/63 (17%)	4/69 (6%)
Three-component seroconversion (week 68) (CSR Table 26)	11/63 (17%)	6/69 (9%)
Three-component seroconversion by week 52, sustained through week 68 (CSR Table 27)	7/63 (11%)	2/69 (3%)
HB e antigen loss (week 52) (CSR Table 31)	21/66 (32%)	8/71 (11%)
Sustained e antigen loss by week 52 (CSR Table 33)	15/66 (23%)	7/71 (10%)
HB s Ag loss (CSR Table 39; see comments in next section)	1/66 (2%)	0
HBV DNA below assay limit on at least one occasion by week 52 (CSR Table 40)	62/63 (98%)	23/69 (33%)
HBV DNA response sustained through week 52 (CSR Table 41)*	28/63 (44%)	11/69 (16%)
HBV DNA response sustained through week 68 (CSR Table 42)	14/63 (22%)	12/69 (17%)
Median percent change in HBV DNA at week 52 (CSR Table 44)	-95	-40
HBV DNA breakthrough by week 52 (CSR Table 45)**	29/57 responders (51%)	8/18 responders (44%)
HBV DNA relapse after week 52, by week 68 (CSR Table 47)	17/28 sustained responders (61%)	3/11 sustained responders (27%)
ALT normalization by week 52 (at least 2 consecutive visits) (CSR Table 48)	44/66 (67%)	16/68 (24%)
ALT breakthrough by week 52 (CSR Table 51)	17/44 (39%)	9/14 (64%)
ALT relapse after week 52 (CSR Table 52)	13/27 (48%)	1/5 (20%)

\* "Sustained HBV DNA response is defined to occur when HBV DNA measurements below the lower limit of detectability have been reported for 2 consecutive visits with no 2 subsequent consecutive measurements (or a single measurement at last visit) above the lower limit of detectability through to week 52." \*\* "HBV DNA breakthrough is said to occur after an HBV DNA response (for at least 2 consecutive measurements) if at least 2 consecutive measurements at least 7 days apart (or a single measure at week 52) above the lower limit of detectability have occurred and no 2 consecutive HBV DNA measurements below the lower limit of detectability have occurred again through to the 52 week period."

### III-A3. NUCA3010 Efficacy Results (FDA Comments)

The FDA analysis focused on the protocol-defined primary endpoint of at least a two-

point improvement in the total Knodell score, and the principal secondary endpoint of week 52 three-component seroconversion. Subjects who did not have a baseline Knodell score in the dataset were excluded from analysis of the histologic endpoint, and subjects who had negative baseline e antigen or baseline HBV DNA below the assay limit were excluded from the seroconversion analysis. Please see the Statistical Review for additional comments on methodology and outcomes. Results are shown in Table 2. Differences between lamivudine and placebo were found for both analyses ( $p=.001$  for histology,  $p=.036$  for seroconversion). The seroconversion analysis was sensitive to the treatment of missing values.

Table 2. NUCA3010, principal endpoints

Week 52 Outcome	Lamivudine	Placebo
Histologic improvement	N=62	N=62
Yes	55%	25%
No	27%	59%
Missing data	18%	16%
Seroconversion criteria met	N=63	N=69
Yes	17%	6%
No	67%	78%
Missing data	16%	16%

Changes between week 52 (end of treatment) and week 68 (end of follow-up) were evaluated to assess durability of treatment response, as described in the Statistical Review. In the lamivudine group, the proportion of subjects meeting seroconversion criteria was the same at the end of treatment and after four months off treatment, but the successes were not all the same subjects at the two time points. In the placebo group, subjects meeting seroconversion criteria at week 52 also met the criteria at week 68, and two additional subjects met criteria at week 68. The differences in treatment effect between week 52 and week 68 reflected changes in a very small number of subjects. HBV DNA re-emergence during treatment, emergence of HBV YMDD mutations associated with reduced drug susceptibility, and endpoints associated with these events are described in section VI below.

Appendix 8.12 (Serology data) yielded two subjects with a value of Undetectable listed for HB s Ag at week 24. Subject 9974 had a subsequent value of Detectable at a Withdrawal visit dated a little more than five months after the 24 week value. Subject 10167 was excluded from the Intent-to-Treat population, with multiple inclusion/exclusion criteria violations listed in Appendix 8.1 including violation of inclusion criterion 2 (HB s Ag detectable in serum for at least once at least 6 months before screening and at screening). Therefore, no case was found in this study with documented chronically positive HB s Ag becoming repeatedly negative in a context suggestive of treatment effect.

### III-A4. NUCA3010 Safety Results (Summary of Applicant's Analysis)

No deaths were reported. Two patients were withdrawn due to adverse events, both with psychiatric manifestations including suicidal ideation or attempt, both considered unrelated to study therapy, one in the lamivudine group and one in the placebo group. The overall adverse event profile was similar in the lamivudine and placebo groups. Grade 3 and/or 4 laboratory toxicities (section 10.4) occurred in 51% of lamivudine-treated subjects and 37% of placebo-treated subjects and included glucose, transaminase, CPK, and lipase elevations; during-treatment ALT elevations were similar between the two treatment groups. After-treatment grade 3 and/or 4 laboratory toxicities were reported as occurring in a slightly higher proportion of lamivudine than placebo subjects (29% versus 14%), and as being attributable to grade 3 toxicities. Post-treatment grade 3 and/or 4 ALT elevations occurred in 25% of lamivudine subjects and 8% of placebo subjects; of those experiencing these elevations, 69% in the lamivudine group and 60% in the placebo group declined to grade 2 or less by the end of the study. Additional analyses were carried out for abnormal liver function tests during and after treatment and are summarized in Table 3 (data from CSR Tables 90 and 91). Relationships of ALT elevations to ethnicity and to seroconversion were also examined and no clear relationships or conclusions were identified. Transaminase elevations were reported to be temporally associated with symptoms in three lamivudine subjects.

Table 3. Liver function test elevations, NUCA3010

Event	Lamivudine group	Placebo group
<b>During therapy:</b>		
ALT ≥ 2x baseline	18/70 (26%)	19/71 (27%)
ALT ≥ 3x baseline	7/70 (10%)	9/71 (13%)
ALT ≥ 2x baseline & >500	1/70 (1%)	7/71 (10%)
ALT ≥ 2x baseline and bilirubin ≥ baseline and >2x ULN	0	0
<b>After treatment:</b>		
ALT ≥ 2x baseline	19/65 (29%)	13/66 (20%)
ALT ≥ 3x baseline	16/65 (25%)	5/66 (8%)
ALT ≥ 2x baseline & >500	12/65 (18%)	6/66 (9%)
ALT ≥ 2x baseline and bilirubin ≥ baseline and >2x ULN	1/65 (2%)	1/66 (2%)

### III-A5. NUCA3010 Safety Results (FDA Comments)

Common adverse events showing at least 5% excess in the lamivudine group over the placebo group, according to the listings in the clinical study report, are listed in Table 4. Laboratory adverse events (grade 3 and/or 4 toxicities) suggesting differences between the treatment groups are listed in Table 5.

Table 4. Common adverse events with at least 5% excess in lamivudine group (from CSR Table 67)

Event	% of lamivudine subjects (n=70)	% of placebo subjects (n=71)
Malaise & fatigue	47%	38%
Nasal signs & symptoms	14%	7%
Arthralgia & articular rheumatism	13%	8%
Cough	11%	6%
Sexual function disorders	6%	1%
Abnormal LFTs	6%	1%
Hypertension	6%	1%
GI signs and symptoms	6%	0%

Table 5. Selected laboratory adverse events (from CSR Table 77)

Event	% of lamivudine subjects (n=70)	% of placebo subjects (n=71)
ALT>3x baseline	33%	14%
CPK≥7x baseline	10%	7%
Lipase>2.5xULN	10%	7%

Case report forms (CRFs) were reviewed for the two patients withdrawn because of adverse events. Bipolar disorder and multiple personality disorder were noted as pre-existing conditions at entry in one patient discontinued from placebo because of psychiatric symptoms. No prior psychiatric diagnosis was noted on the history form for the other patient, discontinued from lamivudine following a suicide attempt.

### III-A6. Summary of Study NUCA3010

The principal histologic endpoint showed a substantial treatment difference between lamivudine and placebo. The difference in proportion of subjects meeting seroconversion criteria at week 52 was less robust statistically as well as lower in magnitude than the histologic difference. No treatment effect was shown in the very small number of African-American patients: as the number enrolled is too small to draw any conclusions about whether there is a difference in response in this population, and little supporting information is available from the other principal phase III studies (see below), this area was proposed for further examination in phase IV studies. A substantial proportion of lamivudine subjects who experienced decline in HBV DNA below the assay limit had re-emergence of assay-positive HBV DNA during treatment. Seroconversion status was inconsistently maintained following cessation of therapy, and a substantial subgroup of patients experienced transaminase abnormalities following cessation of lamivudine. Otherwise, no major new clinical adverse events were reported relative to the safety profile of lamivudine in previous studies. Grade 3 and/or 4 elevations of CPK and of lipase were more frequent in lamivudine subjects than in placebo subjects, but were not reported as associated with frequent clinical abnormalities.

### III-B. Clinical Study NUCAB3011

Protocol NUCAB3011, "A placebo controlled study of lamivudine and Intron A® in patients with chronic hepatitis B infection who are interferon α non-responders," was submitted to [REDACTED]. The CSR was submitted [REDACTED].

### III-B1. NUCAB3011 Study Design

Study NUCAB3011 enrolled 238 subjects from 63 centers in eleven countries. This was a randomized partially-blinded study with a placebo control for lamivudine but not for interferon. Eligible subjects had received a cumulative total of at least 240 million units of interferon alpha, at least 6 months before screening, and had ongoing evidence of active chronic hepatitis B as documented by serum HB s Ag, HB e Ag, HBV DNA, and elevated ALT. Subjects were randomized 2:1:1 to receive lamivudine 100 mg/day for 52 weeks; placebo; or lamivudine 100 mg/day for 8 weeks followed by lamivudine plus Intron A® 10 million units subcutaneously three times a week for 16 weeks. At the end of 52 weeks, subjects in the lamivudine group were re-randomized to receive lamivudine or placebo for a further 16 weeks. Primary analyses compare treatment response at the 52 week time point. The primary endpoint was histologic response (improvement of 2 or more points in Knodell HAI score). For analysis of week 52 responses, all subjects randomized to an initial 52 weeks of lamivudine (i.e. either 52 weeks total lamivudine or 68 weeks total lamivudine) were considered as one group. For analyses of events during follow-up, subjects randomized to 52 weeks of lamivudine followed by 16 weeks of placebo (LAM/PLA) were considered as one treatment group and subjects randomized to 68 weeks of lamivudine (LAM/LAM) were considered as a separate group.

### III-B2. NUCAB3011 Efficacy Results (Summary of Applicant's Analysis)

Of 238 patients randomized, 132 (55%) were at U.S. centers. The remainder were enrolled in Portugal (18), Turkey (15), Canada (15), Germany (13), Czech Republic (11), U.K. (8), Spain (8), Netherlands (7), Israel (6), and Poland (5). Of subjects randomized to 68 weeks of lamivudine, fifteen reportedly did not take lamivudine between weeks 52 and 68 "because they withdrew or were found to have developed HB e Ab by week 48." Principal efficacy analyses used the treatment groups to which patients were assigned by randomization. Gender and ethnicity distribution differed somewhat across groups, as shown in Table 6 (data from CSR table 6). Routes of HBV acquisition included sexual contact (32%), unknown (34%), vertical/perinatal (12%), transfusion (8%), intravenous drug use (<1%), and other (14%). Selected outcome measures are listed in Table 7.

Table 6. Demographic distribution of NUCAB3011 subjects

CSR-defined category	Lamivudine monotherapy	Lamivudine + interferon	Placebo	Total
Female (n, %)	20/119 (17%)	18/63 (29%)	7/56 (13%)	45/238 (19%)
Caucasian/White	93 (78%)	52 (83%)	49 (88%)	194 (82%)
Negroid/Black	6 (5%)	2 (3%)	0	8 (3%)
Oriental	11 (9%)	5 (8%)	3 (5%)	19 (8%)
Asian (Not Oriental)	3 (3%)	0	2 (4%)	5 (2%)
Hispanic	5 (4%)	2 (3%)	0	7 (3%)
Other	1 (<1%)	2 (3%)	2 (4%)	5 (2%)

Table 7. Selected principal and subsidiary endpoints, NUCAB3011

Week 52 Outcome	Lamivudine	Combination	Placebo
HAI decrease $\geq$ 2 points (CSR Table 16)	62/119 (52%)	20/63 (32%)	14/56 (25%)
Necroinflammatory improvement (ranked response) (CSR Table 17)	63/119 (53%)	21/63 (33%)	16/56 (29%)
Fibrosis worsening (ranked response) (CSR Table 17)	4/119 (3%)	8/63 (13%)	3/56 (5%)
HB e Ag seroconversion (CSR Table 23)	19/108 (18%)	7/57 (12%)	7/53 (13%)
HB e Ag loss (CSR Table 29)	38/116 (33%)	13/63 (21%)	7/54 (13%)
HB s Ag seroconversion (CSR Table 32)	0	1/63 (2%)	0
HB s Ag loss (CSR Table 35)	2/119 (2%)	4/63 (6%)	0
HBV DNA below assay limit at least once by week 52 (CSR Table 38)	102/110 (93%)	56/57 (98%)	23/54 (43%)
HBV DNA response sustained to week 52 (CSR Table 39)	60/110 (55%)	13/57 (23%)	9/54 (17%)
HBV DNA breakthrough by week 52 (CSR Table 43)	27/98 (28%)	33/48 (69%)	1/16 (6%)
ALT response by week 52 (CSR Table 45)	72/115 (63%)	27/62 (44%)	14/54 (26%)
ALT response sustained through week 52 (CSR Table 46)	51/115 (44%)	11/62 (18%)	8/54 (15%)
HBV DNA response plus e Ag loss (CSR Table 49)	29/108 (27%)	9/57 (16%)	7/53 (13%)

Histologic responders were distributed somewhat unequally between U.S. sites (40/68, 59%) and non-U.S. sites (22/51, 43%). The two groups formed by secondary

randomization at week 52 had an imbalance in the proportion with baseline positive HBV DNA and HB e Ag assays (58/60, 97% in LAM/LAM group, 50/59, 85% in LAM/PLA group,  $p=.029$ ). Week 68 seroconversion was reported for 14/58 (24%) LAM/LAM, 7/50 (14%) LAM/PLA, 7/53 (13%) placebo, and 5/57 (9%) combination patients. ALT and HBV DNA breakthrough by week 68 were more common in LAM/PLA than LAM/LAM subjects (CSR Tables 43, 48). Logistic regression analysis using baseline hepatic and demographic descriptors did not show major interactions for week 52 histologic response except that differences between lamivudine monotherapy and combination therapy decreased at higher baseline ALT. For week 52 seroconversion, gender and weight (but not body mass index) showed significant interactions, and for week 68 seroconversion there were significant interactions with baseline HBV DNA and weight; the meaning of these interactions was considered unclear due to small numbers and multiple analyses.

### III-B3. NUCAB3011 Efficacy Results (FDA Comments)

Principal endpoints were analyzed in the same manner as for the other principal phase III studied (see Statistical Review and Table 8). The treatment effect for the comparison of lamivudine versus placebo for the principal histologic endpoint ( $p=.001$ ) was similar to results in the other placebo-controlled studies, NUCB3009 and NUCA3010. When the LOCF convention was not used to impute HB e Ag and HB e Ab results, no appreciable difference was seen between lamivudine and placebo in the seroconversion endpoint.

Table 8. Principal endpoints, NUCAB3011

Week 52 Outcome	Lamivudine	Placebo
Histologic improvement	N=110	N=54
Yes	56%	26%
No	25%	54%
Missing data	19%	20%
Seroconversion criteria met	N=108	N=53
Yes	15%	13%
No	67%	68%
Missing data	17%	19%

Comparisons of week 52 and week 68 seroconversion status are outlined in the Statistical Review. Although a higher proportion of subjects randomized to 68 weeks of lamivudine met seroconversion criteria at week 68 than in the group randomized to 52 weeks of lamivudine followed by 16 weeks of placebo, there was a divergence between these two groups in proportion meeting seroconversion criteria at week 52 when there was no treatment difference, which appeared to explain part of the week 68 difference. Due to the small numbers of seroconverters, no conclusions could be drawn about the effect of continuing lamivudine for the additional 16 weeks or about durability of seroconversion.

In the group of patients receiving lamivudine monotherapy, the proportion of subjects with e antigen loss at week 52 was substantially larger than the proportion of subjects

who met three-component seroconversion criteria at week 52. This discrepancy was much larger in the lamivudine monotherapy group than in either of the other initial treatment groups. To explore whether these treatment-related differences between e antigen loss and three-component seroconversion were a general feature of lamivudine treatment, the same relationships were examined in the other three principal phase III studies. Comparable relationships were not found. Re-emergence of HBV DNA during therapy and development of YMDD mutations are summarized in section VI below.

The combination therapy arm showed no evident advantage over lamivudine monotherapy (Table 9). It was not possible to determine whether the study design provided an appropriate comparison between these treatment options (see NUCB3010).

Table 9. NUCAB3011 outcomes including combination treatment group

Week 52 outcome	Histologic endpoint (n=110 lamivudine, 59 combination, 54 placebo)	Seroconversion endpoint (n= 108 lamivudine, 57 combination, 53 placebo)
Lamivudine successes	56%	15%
Combination successes	34%	5%
Placebo successes	26%	13%

In gender comparisons, very similar response rates for males and females were reported for each treatment group for the principal histologic endpoint (Table ST-27 of CSR). There are difficulties in considering results across studies, or across centers within this study, regarding differences between ethnic groups, because the definitions used to collect information and the distribution of subjects were not uniform. "Hispanic" was recorded as a category only in the U.S. centers for this study. As in other reports submitted by the applicant, records from non-U.S. sites classified subjects as "Oriental" if they were of East Asian origin and as "Asian (Not Oriental)" if from other parts of Asia (e.g. India), but the "Asian (Not Oriental)" category was not used at U.S. sites. In NUCAB3011, only 8 subjects were classified as "Negroid/Black" (or "Black"): none of these received placebo, six received lamivudine monotherapy, and 2 received combination therapy, so no comparison of lamivudine versus placebo could be performed. However, 5 of the 6 subjects designated as Black and as receiving lamivudine monotherapy were reported as histologic responders (numerically higher than other categories in this study: 5 of 11 in the Oriental category, 46 of 93 in the Caucasian category, and 6 of 9 in the Other category), while the sixth was listed as "missing"; and neither of the 2 subjects designated as Black and receiving combination therapy was classified as a responder. Specific results for the Black category from the NUCA3010 study report and the NUCAB3011 study report are summarized in Table 10. Although no conclusions about treatment effect can be drawn from these small numbers, the two studies together do not suggest a reproducible lack of effect relative to other treatment groups. Confirmation of effects in different populations is one of the topics identified as potential phase IV commitments.

Table 10. Histologic responses in subjects classified as "Black", NUCA3010 and NUCAB3011

Treatment	Lamivudine	LAM/IFN	Placebo
NUCA3010 Total classified in Black category (Table ST12)	10	—	13
Responder (HAI decrease $\geq$ 2 points)	3	—	5
No change	2	—	1
Worsened	2	—	4
Missing	2	—	2
NUCAB3011 Total classified in Black category (Table ST28)	6	2	0
Responder	5	0	0
No change	0	0	0
Worsened	0	1	0
Missing	1	1	0

#### III-B4. NUCAB3011 Safety Results (Summary of Applicant's Analysis)

No deaths were reported. For purposes of safety analysis, subjects randomized to LAM/LAM but not continued on lamivudine after week 52 were included in the LAM/PLA group instead of in the randomized treatment assignment used for efficacy analyses; therefore, totals in the two groups are different in the efficacy analyses and the safety analyses. Overall adverse events were reported as being most common in the lamivudine/interferon combination therapy group, with the most common adverse events characteristic of interferon-associated adverse events. Adverse event profiles were reported as comparable between the lamivudine monotherapy and placebo groups, with no proportionate increase in adverse events associated with 68 weeks compared with 52 weeks of lamivudine, and with the most common adverse events in these groups characteristic of the underlying disease. Serious adverse events described in the report (section 10.3.6) as "likely to be associated with the underlying disease" included exacerbation of hepatitis (one subject in LAM/LAM group), increased transaminases (one subject in placebo group and two in LAM/PLA group), increased lipase (one subject in LAM/PLA group), increased CPK (one subject in LAM/PLA group), and hepatic encephalopathy (one subject in placebo group). Four of these events in two patients ("hepatitis flare" on day 28 and jaundice on day 36, subject 4513, LAM/LAM; elevated lipase on day 119 and day 203, subject 4558, LAM/PLA) were recorded by investigators as almost certainly related to study drug; there were also four serious adverse events recorded as probably related to study drug, two in the LAM/PLA and two in the combination therapy arm. There were six withdrawals due to adverse events, four in the placebo group (neuralgia/myalgia, HIV seropositivity, questionable exacerbation of hepatitis, retinal detachment), one on lamivudine monotherapy (stroke), one on combination therapy (fatigue and decreased appetite).

Among grade 3 or 4 laboratory toxicities, ALT elevations were reported to be most frequent in treatment groups which received and stopped lamivudine (LAM/PLA or combination therapy). ALT toxicities were noted to be similar in the LAM/LAM and PLA arms and were attributed to underlying disease. Decreases in neutrophils, hemoglobin, and platelets during combination therapy were noted. Additional analyses (section 10.4.2.3) of ALT elevations are summarized below. No clear relationship between ALT elevations and seroconversions was reported.

Table 11. Liver function abnormalities, baseline to week 52 (active treatment for lamivudine monotherapy, on and post-treatment for combination)

Treatment	Lamivudine	Placebo	Combination
ALT ≥ 2x baseline	31/119 (26%)	11/56 (20%)	30/63 (48%)
ALT ≥ 3x baseline	20/119 (17%)	7/56 (13%)	13/63 (21%)
ALT ≥ 2x baseline & >500	9/119 (8%)	4/56 (7%)	8/63 (13%)
ALT ≥ 2x baseline & bili > 2xULN & ≥ 2x baseline	0	0	0

Table 12. Liver function abnormalities, week 52 to week 68 (active treatment for LAM/LAM, immediately post-treatment for LAM/PLA, late post-treatment for combination)

Treatment	LAM/LAM	LAM/PLA	Placebo	Combination
ALT ≥ 2x baseline	6/44 (14%)	17/67 (25%)	7/47 (15%)	4/53 (8%)
ALT ≥ 3x baseline	3/44 (7%)	13/67 (19%)	4/47 (9%)	2/53 (4%)
ALT ≥ 2x baseline & >500	3/44 (7%)	9/67 (13%)	2/47 (4%)	1/53 (2%)
ALT ≥ 2x baseline & bili > 2xULN & ≥ 2x baseline	1/44 (2%)	0	0	0

### III-B5. NUCAB3011 Safety Results (FDA Comments)

Tables 13 and 14 list common adverse events showing at least 5% excess in the lamivudine monotherapy groups over the placebo group, and selected laboratory adverse events (grade 3 and/or 4 toxicities). Review of CRFs for subjects discontinued due to adverse events did not provide any noteworthy additional information.

Table 13. Common adverse events with at least 5% excess in lamivudine group (from CSR Table 62)

Event	% of lamivudine subjects (n=119)	% of placebo subjects (n=56)
Headache	27%	21%
Abdominal discomfort & pain	21%	14%
Muscle pain	18%	11%
Diarrhea	16%	11%
Arthralgia & articular rheumatism	12%	5%
Abnormal enzyme levels	12%	7%
Throat & tonsil discomfort & pain	10%	5%
Sleep disorders	8%	2%



and weight (mean and median 62 kg) were reasonably balanced across treatments. There were 12 subjects with at least one major protocol violation (6 lacking at least 3 months of HBV DNA  $\geq 5$ , and 6 who took less than 75% of study drug). Principal routes of hepatitis B acquisition were "unknown" (60%) and vertical/perinatal (39%). HB e Ag was undetectable at baseline in one subject, and HB e Ab was detectable at baseline in eight subjects (2 placebo, 6 lamivudine 100 mg).

Table 15. Selected principal and subsidiary endpoints, NUCB3009

Outcome	Lamivudine 100 mg	Lamivudine 25 mg	Placebo
Stratum 1: $\geq 1$ point decrease in necroinflammatory score (CSR Table 20)	72/100 (72%)	70/100 (70%)	19/49 (39%)
Stratum 2: $\geq 1$ point decrease in necroinflammatory score (CSR Table 21)	20/43 (47%)	12/42 (29%)	5/23 (22%)
Strata 1 and 2: $\geq 2$ point decrease in necroinflammatory score (CSR Table 23)	80/143 (56%)	70/142 (49%)	18/72 (25%)
Median change in Knodell score (CSR Table 30)	-3	-2	1
Fibrosis worsened on ranked response (CSR Table 34)	3/143 (2%)	6/142 (4%)	8/72 (11%)
Reduction in HB c antigen and/or HBV DNA on biopsy (CSR Table 37)	81/143 (57%)	74/142 (52%)	40/72 (56%)
Reduction in serum HBV DNA below assay limit, sustained to week 52 (CSR Table 39)	95/140 (68%)	52/135 (39%)	11/70 (16%)
Reduction in HBV DNA below assay limit at any time (CSR Table 38)	134/140 (96%)	98/135 (73%)	16/70 (23%)
DNA breakthrough after fall below assay limit (CSR Table 40; 1-occasion definition)	39/134 (29%)	46/98 (47%)	5/16 (31%)
Loss of e antigen at week 52 (missing values imputed using LOCF) (CSR Table 43)	25/143 (17%)	25/142 (18%)	5/71 (7%)
3-component HB e Ag seroconversion at week 52 (missing e Ag and e Ab imputed using LOCF) (CSR Table 45)	22/140 (16%)	17/135 (13%)	3/70 (4%)
HB s Ag (CSR section 8.4.8)	0	0	0
Sustained ALT normalization from abnormal baseline (CSR Table 51)	68/95 (72%)	64/98 (65%)	12/50 (24%)

Table 15 summarizes major components of the analysis. Both doses of lamivudine were associated with higher likelihood of histologic improvement at week 52 than placebo, with overall response rates lower in the mild hepatitis group (stratum 2) than in the moderate/severe group (stratum 1) for all three treatments. Lamivudine 100 mg was associated with reduced progression of fibrosis on ranked biopsies. Reduction of

hepatitis B markers in the liver was not markedly enhanced by lamivudine. Subjects receiving 100 mg lamivudine were more likely to have a fall in HBV DNA below the assay limit than the 25 mg group or the placebo group, while the 25 mg group was intermediate between the 100 mg and placebo groups. Seroconversion and ALT normalization were more common in the lamivudine 100 mg than the placebo group, and the 25 mg group also had more ALT normalization than the placebo group.

### III-C3. NUCB3009 Efficacy Results (FDA Comments)

The FDA efficacy analysis focused on the principal endpoints and analysis methods used across the principal phase III studies, for the comparison between lamivudine 100 mg daily and placebo. Principal results are shown in Table 16. Seroconversion successes were much less common than histologic successes for each treatment group. However, lamivudine 100 mg/day showed an advantage over placebo for each of the principal endpoints ( $p=.001$  for histology,  $p=.017$  for seroconversion). Additional analyses of relationships between endpoints, endpoint components, changes over time, and endpoints associated with viral re-emergence and viral mutations are summarized in section VI.

Table 16. Principal endpoints, NUCB3009

Week 52 Outcome	Histology (lamivudine, n=131)	Histology (placebo, n=68)	Seroconversion (lamivudine, n=140)	Seroconversion (placebo, n=70)
Success	56%	26%	16%	4%
Failure	36%	62%	80%	91%
Missing	8%	12%	4%	4%

### III-C4. NUCB3009 Safety Results (Summary of Applicant's Analysis)

No deaths were reported. Adverse events were reported for 77% of subjects in the placebo and 25 mg lamivudine groups and 80% of subjects in the 100 mg lamivudine group. The overall distribution was similar in the various treatment groups and the only difference noted as statistically significant is for ear, nose, and throat infections (greater in lamivudine 25 mg group than in placebo group). There were three pregnancies during the study and these patients were withdrawn; the infant born to a patient in the 100 mg lamivudine group was reported to have cardiac dysrhythmia and mild mitral valve prolapse. Two other subjects were withdrawn due to adverse events, one because of elevated CPK and one because of diarrhea, both in the lamivudine 100 mg group. No patterns of laboratory abnormalities suggestive of drug association were noted.

### III-C5. NUCB3009 Safety Results (FDA Comments)

Table 17 lists common adverse events identified as showing at least 5% excess in the lamivudine 100 mg group compared with the placebo group.

Table 17. Selected common clinical adverse events (from CSR Table 56)

Event	% of lamivudine subjects (n=143)	% of placebo subjects (n=73)
Diarrhea	17%	10%
Throat & tonsil discomfort & pain	16%	8%
ENT infections	13%	4%
Nausea & vomiting	8%	1%

From the electronic dataset, 8% of 100 mg lamivudine subjects were identified as having at least one CPK value  $\geq$  7 times baseline, compared with 3% of placebo subjects, a comparison made to provide uniformity with analyses of other studies. Lipase was not monitored in this study. Review of CRFs for subjects discontinued due to adverse events revealed a pattern of gradually progressive CPK elevation in the one subject (number 3014) discontinued from lamivudine 100 mg/day for that reason, followed by a gradual decline after drug cessation (individual visit laboratory values were included in the CRF for this subject). Additional safety comments from follow-on study information are included below in the discussion of study NUCB3018.

### III-C6. Summary of Study NUCB3009

In study NUCB3009, recipients of lamivudine 100 mg/day for 52 weeks showed more histologic responses and more seroconversions than placebo recipients, although the number of seroconversion responses overall was small. Thus, study results suggested a significant treatment effect on both principal endpoints. The treatment group receiving lamivudine 25 mg/day appeared more similar to 100 mg/day on some outcome measures and intermediate between placebo and 100 mg on other measures. No new safety concerns were identified in this study relative to the known safety profile of lamivudine in the treatment of HIV infection.

### III-D. Clinical Study NUCB3010

This international, multicenter, partially blinded study is entitled "A study of lamivudine and alpha-interferon in patients with chronic hepatitis B infection who are interferon treatment naïve." Study NUCB3010 enrolled 230 patients at 51 centers in 15 countries. The CSR was submitted to \_\_\_\_\_.

#### III-D1. NUCB3010 Study Design

Patients eligible for this study had positive hepatitis B surface antigen on at least one occasion at least 6 months before screening; positive e antigen at least once 3 or more months before screening; positive HBV DNA at least once 3 or more months before screening; and ALT at least 1.3 times the upper limit of normal (but less than 10 times the upper limit of normal) at least once 3 or more months before screening. Subjects were randomized to 3 treatment arms in a 1:1:1 ratio. The first 8 weeks of treatment were

blinded, but subsequent treatment included interferon injections for 2 of the treatment arms without an interferon placebo in the other arm. Study treatments were 52 weeks of lamivudine 100 mg/day followed by 12 weeks off-treatment follow-up; 8 weeks of placebo followed by 16 weeks of placebo plus alpha interferon followed by 40 weeks off-treatment follow-up; or 8 weeks of lamivudine followed by 16 weeks of lamivudine plus alpha interferon followed by 40 weeks off-treatment follow-up. The primary endpoint was three-component hepatitis B e antigen seroconversion at week 52. Secondary endpoints included histologic response, individual serologic and virologic markers, and transaminase normalization.

### III-D2. NUCB3010 Efficacy Results (Summary of Applicant's Analysis)

Of 310 patients screened, 230 were randomized, and the modified intent-to-treat population (all randomized subjects with confirmed chronic hepatitis B) consisted of 226 subjects (82 lamivudine, 69 interferon, 75 combination). In nine instances, actual treatment did not match the randomized assignment (one lamivudine monotherapy subject who received two doses of interferon; one stated to have been "mis-randomised"; seven reported to have received erroneous dispensing or withholding of interferon at week 8 who were continued on their week 8 de facto treatment, including two interferon monotherapy subjects who were not dispensed interferon and were withdrawn from the study). Primary efficacy analyses follow the randomized assignments. Baseline age, weight, height, and route of hepatitis B acquisition were reasonably balanced across treatment groups, while the interferon monotherapy group had somewhat fewer women (19% versus 29% in the other two groups) and non-Oriental Asians (1% versus 9% and 12% in the other two groups). Overall the study population was described as 74% male; 63% Caucasian/white, 4% Negroid/Black (including 2 lamivudine monotherapy subjects, both nonresponders on histology and seroconversion, CSR Tables ST13 and ST15), 22% Oriental, 8% non-Oriental Asian, 0% Hispanic, and 4% Other (see discussion of NUCAB3011 regarding definitions of ethnicity); mean age 34, median 31, range 15-70 years; probable route of hepatitis B acquisition 2% IV drug use, 17% sexual contact, 2% transfusion, 55% unknown, 12% vertical/perinatal, 12% other. Variation in baseline hepatitis characteristics between treatment groups is summarized in Table 18. Baseline ALT, albumin, and bilirubin were reported as similar across groups.

Table 18. Baseline hepatitis characteristics, NUCB3010 (from CSR section 7.5.3)

Treatment group	Lamivudine	Interferon	Combination
% with cirrhosis	6%	12%	4%
Median HBV DNA	136 pg/ml	109 pg/ml	94 pg/ml

Selected outcome measures at week 52 are summarized in Table 19. The difference in seroconversion between lamivudine monotherapy and combination therapy was stated to be statistically significant ( $p=.011$ ) in a "per protocol" comparison but not in the intent-to-treat analysis. Females were more likely to seroconvert than males in the combination group (11/19 versus 9/49) but the opposite was reported for the lamivudine monotherapy