CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22011
Drug Name:	β-L-Thymidine (L-Thymidine, LdT)
Indication(s):	Carcinogenicity in 104 weeks in rats and 26 weeks in mice
Applicant:	[redacted] submitted for Index Pharmaceuticals, Inc.
	Cambridge, Massachusetts
Documents Reviewed:	Electronic submission of study reports, Received date Dec. 30, 2005 Data submitted electronically
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
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Project Manager:	Kenny Shade
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of L-Thymidine when administered orally through gavage with appropriate drug levels in regular rats for 104 weeks and in transgenic mice for 26 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Yuen.

2. Rat Study

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated and one control group. Two hundred and sixty Ctr:CD®(SD)IGS BR rats of each sex were randomly allocated to treated groups and control groups in equal size of 65 animals. The dose levels for treated groups were 500, 1000, and 2000 mg/kg/day. In this review these dose groups will be termed as the Low, Medium, and High dose groups, respectively. The control received the vehicle, (0.5% carboxymethylcellulose) through gavage. The animals were initially intended to be treated for 104 weeks, however, due to excessive mortality dosing of high dose group was ceased at Week 85. The surviving animals of all treatment groups were sacrificed during Weeks 95 – 96, when the survival in every group reached about 50%.

The animals were observed twice daily for mortality and morbidity. A detailed clinical observation was performed on each animal once weekly. A complete histopathological examination was performed on all animals found dead, killed moribund, or sacrificed during or at the end of the experiment. Body weights were taken during the initiation of the study and weekly during the first 14 weeks of the study, and every 4 weeks thereafter.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Tests of survival data included graphical representation of survival distributions using the Kaplan-Meier curves, Cox-Tarone binary regression methods for trend and heterogeneity analysis, and Gehan-Breslow non-parametric methods for trend and heterogeneity analysis.

Sponsor's analysis showed that by the end of Week 85, survival rates in the control, low, medium, and high dose groups were 55%, 42%, 47%, and 38%, respectively in males and 49%, 45%, 52%, and 38%, respectively in females. At terminal sacrifice the survival rates were 38%, 25%, 25%, and 31%, respectively in males and 34%, 28%, 34%, and 23%, respectively in females. The sponsor's analysis did not show statistically significant dose response in mortality in any sex. The 500 and 2000 mg/kg/day dose group showed statistically significant increased mortality in males. No such statistically significant increased mortality was observed in any treated group in females.

Reviewer's comment: This reviewer's calculation showed the percentages of survival at terminal sacrifice in control, low, medium, and high dose groups as 40%, 25%, 28%, and 34%, respectively for males, and 34%, 28%, 34%, and 26%, respectively for females. As seen these rates differs slightly from sponsor's calculation.

2.1.2. Tumor data analysis

Incidental tumors were analyzed by Dinse-Lagakos logistic prevalence methods for trend and heterogeneity. Rapidly lethal and palpable tumors were analyzed in the same manner as survival. In cases where the study pathologist could assign particular occult neoplastic lesions as the cause of death , such information was

taken into the analysis. In cases of sparse tables, exact form of survival adjusted method of tumor analysis was used.

Sponsor's analysis showed no evidence of increased oncogenicity associated with the administration of the test material. The most prevalent neoplasms present included pituitary adenomas, pheochromocytomas, thyroid c-cell adenomas and mammary gland fibroadenomas and carcinomas. An increased incidence of pancreatic acinar cell adenomas was noted in the male rat group given 500 mg/kg/day (3/65 or 4.6%)) and in the group given 2000 mg/kg/day (5/65 or 7.7%), while none were observed in the control or mid-dose (1,000 mg/kg/day) dose group. The sponsor mentioned that the incidence of this tumor type was slightly higher in the 2000 mg/kg/day males compared to the historical range at [redacted] (0-5%), however, was well within the [redacted] published range of 1.43-11.43%. The sponsor further mentioned that there was no evidence of a dose response between 500 and 2000 mg/kg/day males, and the incidence of pancreatic acinar cell was comparable for all groups (including controls).

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The intercurrent mortality data are given in Tables 1A and 1B for males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 1A and 1B for males and females, respectively. The homogeneity of survival distributions of all five groups was tested separately for males and females using the Cox test (Cox, 1972) and the Generalized Wilcoxon test (Gehan, 1965). Results of the tests are given in Tables 2A and 2B for males and females, respectively. The tests showed no statistically significant differences in survivals across treatment groups in any sex.

2.2.2. Tumor data analysis

Since the sponsor classified the tumor types as 'cause of death' and 'not a cause of death', following Peto et al., (1980), this reviewer applied the 'death rate method' and the 'prevalence method' for these two categories of tumors respectively, to test the dose response[1] relationship. For tumor types occurring in both categories a combined test of 'death rate method' and the 'prevalence method' was performed. For the calculation of p-values, the Exact Permutation method was used. The actual dose levels of treatment groups were used as the weight for the trend analysis. The time intervals used were 0 - 52, 53 - 78, 79 - 91, 92 - 96 weeks, and terminal sacrifice for both sexes. The tumor rates and the p-values of the tumor types tested for dose response relationship are listed in Table 3A and 3B for males and females, respectively. Pairwise comparisons between treated groups and control were also performed using the age adjusted Fisher exact test and are given in Tables 4A and 4B for males and females, respectively.

2.2.3. Multiple testing adjustment

Adjustment for the multiple trend testing was done using the results of Lin and Rahman (1998), which

[1] In this reviewer's analysis the phrase "Dose response" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

recommend to use a significance level of α=0.05 for rare tumors and α=0.01 for common tumors for submissions with one 104 week study. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using the results of Haseman (1983), which recommend to use a significance level α=0.05 for rare tumors and α=0.01 for common tumors.

2.2.4. Reviewer's findings

The following tumor types showed dose response p-values less than or equal to 0.05.

Sex	Organ	Tumor	P-Value
Male	Pancreas	B-Adenoma, Acinar cell	0.0214
Female	Adrenal	B-Pheochromocytoma	0.0438

Based on the results of Lin and Rahman the incidence of acinar cell B-adenoma in pancreas in males was considered to have statistically significant dose response. The pairwise comparison of high dose group with vehicle control for the incidence of acinar cell B-adenoma in pancreas had a p-value of 0.029. However, based on the results of Haseman this was not considered to be statistically significant. No other pairwise comparison was statistically significant in either sex.

Reviewer's comment: The sponsor's pairwise comparison showed a significant increment in the incidence of pancreas acinar cell B-adenoma in high dose group compared to the control in males, however this reviewer's analysis did not show that. Difference in this finding could be because of the following three reasons 1) sponsor did not mention of any adjustment for the multiple testing, when this reviewer did it using the suggested by Haseman, 2) in sponsor's calculation they might not have made any adjustment for mortality difference among treatment groups as was done by this reviewer, and 3) the sponsor might have used the asymptotic p-values compared to the exact p-value as was used by this reviewer. The asymptotic p-value from this reviewer's calculation is 0.0116, which is significant after the adjustment for multiple testing using the method suggested by Haseman.

3. Mouse Study

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated groups and two control groups, known as vehicle control and positive control. One hundred and twenty five CB6F1/Jic-TgrasH2@TAC transgenic mice of each sex were randomly allocated to treated groups and controls in equal size of 25 animals. The dose levels for treated groups were 500, 1000, and 2000 mg/kg/day for L-Thymidine treated groups and 75 mg/kg/day of N-Methyl-N-nitrosourea (MNU) for the positive control. The vehicle control received the vehicle, (0.5% Carboxymethylcellulose-Sodium solution USP) through gavage.

Clinical observations were recorded once daily in the morning, and were initiated on the day following arrival. A mortality check was performed once daily in the afternoon. Upon discovery of a mass during clinical observations, measurements were performed to track the approximate length and width of the mass and recorded. Any lump (mass) less than 4 mm in diameter was not considered to be biologically significant and was not recorded. Tissue masses in excess of 4 mm in diameter were identified by palpation, and their location, size and date were documented. Following this, the daily measurement of a mass was also recorded. Scheduled necropsies were performed on all surviving animals in Week 27. Body weights were measured for all animals upon their receipt following delivery to the facility, on the day before dosing (Day -1), weekly throughout the study, and on the day of necropsy.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Sponsor did not perform any formal statistical analysis of the mortality data. As summary statistics the sponsor reported that the survival rates of Groups 1 to 4 were, 96%, 100%, 100% and 92% respectively, among males, and 80%, 100%, 92% and 92%, respectively in females. The sponsor concluded that no test article-related differences in mortality occurred between control and any of the test article treatment groups.

3.1.2. Tumor data analysis

Sponsor analyzed the histopathology data for incidence of neoplastic and non-neoplastic lesions using the Fisher's exact test for comparing each of the treated groups and positive control group with vehicle control. Sponsor's analysis did not show statistically significant differences in the incidences of any tumor type between the high dose group and vehicle control.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The survival rates were estimated using the Kaplan-Meier product limit method. The homogeneity of survival among vehicle control, low, medium, and high dose groups was tested using the Log-Rank and Wilcoxon tests. The intercurrent mortality data are given in Tables 5A and 5B for males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B for males and females, respectively. Results of the tests for homogeneity of survival among control, low, medium, and high dose groups are given in Tables 6A and 6B for males and females, respectively. The tests showed no statistically significant differences in survivals among vehicle control, low, medium, and high dose groups in either sex. The mortality in the positive control was significantly different.

3.2.2. Tumor data analysis

Positive dose response analysis was performed using the Poly-3 method. The actual dose levels of treatment groups were used as the weight for the trend analysis. The tumor rates and the p-values of the tumor types tested for dose response relationship are listed in Table 7A and 7B for male and females, respectively. Pairwise comparisons between treated groups and vehicle control were performed using the Fisher exact test and are given in Tables 8A and 8B for males and females, respectively.

3.2.3. Multiple testing adjustment

Adjustment for the multiple trend testing was done using a significance level of α=0.05 for rare tumors and α=0.01 for common tumors. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using a significance level α=0.05 for rare tumors and α=0.01 for common tumors.

3.2.4. Reviewer's findings

The reviewer's analyses did not show statistically significant dose response in the incidence of any of the tested tumor types in either sex with respect to vehicle control. Also none of the pairwise comparisons of treated groups with vehicle control was considered to be statistically significant. It may be noted that the pairwise comparisons of the incidences of stomach and skin papillomas in positive control with vehicle control were found to be statistically significant in both sexes.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of L-Thymidine when administered orally through gavage with appropriate drug levels for 104 weeks in rats and for 26 weeks in mice.

In this review, the phrase "dose response" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Rat Study: This study had 4 treatment groups namely, control, 500, 1000, and 2000 mg/kg/day. Due to excessive mortality in rat study, dosing of high dose group was ceased at Week 85 and surviving animals of all treatment groups were sacrificed during Week 95 - 96. The tests showed no statistically significant differences in survivals across treatment groups in either sex. Tests showed statistically significant dose response in the incidence of acinar cell B-adenoma in pancreas in males.

Mouse Study: This study was conducted in CB6F1/Jic-TgrasH2@TAC transgenic mice. This had 5 treatment groups namely, vehicle control, positive control, 500, 1000, and 2000 mg/kg/day. Tests showed no statistically significant differences in survivals across treatment groups. Tests showed no statistically significant dose response in the incidence of any tested tumor types with respect to vehicle control. Pairwise comparison of none of the tested tumor types showed statistically significant increased incidence in the high dose group compared to the vehicle control, however the pairwise comparisons of the incidences of stomach and skin papillomas in positive control with vehicle control were found to be statistically significant in both sexes.

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5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	Control		500 mg/kg/day		1000 mg/kg/day		2000 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %
0 - 52	5	7.7	5	7.7	6	9.2	10	15.4
53 - 78	18	35.4	26	47.7	24	46.2	21	47.7
79 - 91	10	50.8	14	69.2	12	64.6	11	64.6
92 - 94	6	60.00	4	75.4	5	72.3	1	66.2
Term. Sac.	26	40.0	16	24.6	28	27.7	22	33.8

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	Control		500 mg/kg/day		1000 mg/kg/day		2000 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %
0 - 52	3	4.60	6	9.2	3	4.6	3	4.6
53 - 78	24	41.5	21	41.5	24	41.5	25	43.1
79 - 91	14	63.1	13	61.5	10	56.9	18	70.8
92 - 96	2	66.2	7	72.3	6	66.2	2	73.8
Term. Sac.	22	33.8	18	27.7	22	33.8	17	26.2

Table 2A: Intercurrent Mortality Comparison
Male Rats

Method	Test	Statistic	P-value
Cox	Homogeneity	3.30	03472
Kruskal-Wallis	Homogeneity	3.53	0.3170

Table 2B: Intercurrent Mortality Comparison
Female Rats

Method	Test	Statistic	P-value
Cox	Homogeneity	1.70	0.6361
Kruskal-Wallis	Homogeneity	1.43	0.6980

Table 3A: Tumor Rates and Dose Response p-values of Tested Tumors
Male Rat - Treated Over 95 Weeks

Organ	Tumor	Control	500mg	1000mg	2000mg	P-value
ADRENAL, CORTEX	B-ADENOMA	1	0	0	0	1.0000
	M-CARCINOMA	0	1	0	0	0.7378
ADRENAL, MEDULLA	B-PHEOCHROMOCYTOMA	6	3	7	7	0.1620
	M-MALIGNANT PHEOCHROMOCYT	3	0	3	0	0.8713
BONE, OTHER	M-OSTEOSARCOMA	0	1	0	0	1.0000
BRAIN	M-ASTROCYTOMA	0	1	0	1	0.2948
CAVITY, ABDOM	M-CARCINOMA (ENDOCRINE)	0	1	0	0	0.8000
	M-MESOTHELIOMA	0	0	1	0	0.5000
CAVITY, THORACIC	M-SCHWANNOMA	0	1	0	0	------
CORD, THORACIC	M-OLIGODENDROGLIOMA	1	0	1	0	0.7406
HEAD, CORONAL	M-SQUAMOUS CELL CARCINOMA	0	0	1	0	------
HEART	M-ENDOCARDIAL SCHWANNOMA	1	0	0	0	1.0000
	M-MESOTHELIOMA	0	0	1	0	0.5056
HEMATO NEOPLASIA	M-LEUKEMIA, GRANULOCYTIC	0	2	0	0	0.8042
	M-LYMPHOMA	0	1	0	1	0.2871
	M-SARCOMA, HISTIOCYTIC	1	0	2	0	0.6950
KIDNEY	B-LIPOMA	0	1	1	1	0.2834
	M-HEMANGIOSARCOMA	0	0	1	0	0.4894
	M-LIPOSARCOMA	0	0	0	1	0.2683
LIVER	B-ADENOMA, HEPATOCELLULAR	2	0	1	1	0.6644
	M-CARCINOMA, HEPATOCELLUL	2	0	0	0	1.0000
LN, MESENTERIC	M-HEMANGIOSARCOMA	2	0	2	1	0.6074
MAMMARY, MALE	M-CARCINOMA	0	0	1	0	0.5000
NERVE, SCIATIC	M-SCHWANNOMA	1	0	0	0	1.0000
PANCREAS	B-ADENOMA, ACINAR CELL	0	3	0	5	0.0214
	B-ADENOMA, ISLET CELL	3	1	3	3	0.3343
	M-CARCINOMA, ISLET CELL	0	1	1	1	0.2834
PITUITARY	B-ADENOMA	41	32	34	29	0.8832
	M-CARCINOMA	0	1	0	0	0.7288
PROSTATE	M-CARCINOMA	0	0	1	0	0.4890
SALIV GL, MANDIB	M-SCHWANNOMA	0	1	0	0	0.6829
SALIV GL, PARTID	B-HEMANGIOMA	0	0	1	0	------
SKIN, OTHER	B-HEMANGIOMA	0	1	0	0	0.7143
	B-KERATOACANTHOMA	5	1	1	1	0.9045
	B-SQUAMOUS CELL PAPILLOMA	3	0	1	0	0.9567
	M-NEUROFIBROSARCOMA	0	1	0	0	0.6167
	M-OSTEOGENIC SARCOMA	0	1	0	0	0.6167
SPLEEN	M-UNDIFFERENTIATED STROMA	1	0	0	0	1.0000
SUBCUTANEOUS TIS	B-FIBROMA	1	2	2	1	0.1016
	B-LIPOMA	0	1	1	0	0.3273
	M-FIBROSARCOMA	0	1	2	0	0.2033
	M-MALIGNANT SCHWANNOMA	1	0	1	0	1.0000
	M-MYXOSARCOMA	0	0	0	1	0.0667
TESTIS	B-INTERSTITIAL CELL TUMOR	3	3	0	2	0.7734

Table 3A (Continued): Tumor Rates and Dose Response p-values of Tested Tumors
Male Rat - Treated Over 95 Weeks

Organ	Tumor	Control	500mg	1000mg	2000mg	P-value
THYROID	B-"C" CELL ADENOMA	7	7	7	6	0.6163
	B-FOLLICULAR CELL ADENOMA	1	1	2	1	0.5100
	M-"C" CELL CARCINOMA	1	0	1	1	0.2547
	M-FOLLICULAR CELL CARCINO	3	0	1	0	0.9853
TONGUE	M-SQUAMOUS CELL CARCINOMA	0	0	1	0	0.3750
URINARY BLADDER	B-TRANSITNL. CELL PAPILLO	0	0	0	1	0.2340
	M-TRANSITNL. CELL CARCINO	0	2	0	1	0.4438

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Table 3B: Tumor Rates and Dose Response p-values of Tested Tumors
Female Rat - Treated Over 95 Weeks

Organ	Tumor	Control	500mg	1000mg	2000mg	P-value
ADRENAL, CORTEX	B-ADENOMA	1	2	1	1	0.6483
ADRENAL, MEDULLA	B-PHEOCHROMOCYTOMA	1	4	1	6	0.0438
BRAIN	B-GRANULAR CELL TUMOR	0	0	0	1	0.1176
	M-ASTROCYTOMA	0	1	1	1	0.2588
CERVIX	B-GRANULAR CELL TUMOR	1	1	0	2	0.2651
	B-POLYP,ENDOMETRIAL STROM	1	0	0	1	0.4950
	M-SARCOMA,ENDOMETRIAL STR	0	0	0	1	0.2436
CLITORAL GLAND	M-CARCINOMA	0	1	0	0	------
HEAD, CORONAL	M-MALIGNANT AMELOBLASTIC	0	0	1	0	------
	M-SQUAMOUS CELL CARCINOMA	0	0	1	0	------
HEART	M-ENDOCARDIAL SCHWANNOMA	1	0	0	0	1.0000
HEMATO NEOPLASIA	M-LYMPHOMA	0	1	2	2	0.1342
	M-SARCOMA, HISTIOCYTIC	1	2	0	0	0.9297
KIDNEY	B-ADENOMA, TUBULAR CELL	0	0	1	0	0.4937
	B-LIPOMA	0	1	0	0	0.7215
	M-LIPOSARCOMA	0	0	1	0	0.5213
	M-MALIGNANT MESENCHYMOMA	1	0	0	0	1.0000
LIVER	B-ADENOMA, HEPATOCELLULAR	0	0	0	1	0.1176
	M-CARCINOMA, HEPATOCELLUL	0	1	0	0	0.7215
LN, MESENTERIC	M-HEMANGIOSARCOMA	1	0	1	1	0.4931
MAMMARY, FEMALE	B-FIBROADENOMA	19	26	22	26	0.1210
	B-FIBROMA	1	0	0	0	1.0000
	M-CARCINOMA	19	19	14	15	0.8749
	M-FIBROSARCOMA	1	0	0	0	1.0000
OVARY	B-LUTEOMA	1	0	0	0	1.0000
	M-GRANULOSA/THECA CELL TU	1	0	1	1	0.4557
PANCREAS	B-ADENOMA, ACINAR CELL	0	0	1	0	0.4937
	B-ADENOMA, ISLET CELL	0	1	2	0	0.5380
PITUITARY	B-ADENOMA	54	51	54	57	0.1004
	M-CARCINOMA	2	0	1	1	0.6597
SKIN, OTHER	M-NEUROFIBROSARCOMA	0	1	0	0	0.4762
SPLEEN	M-UNDIFFERENTIATED STROMA	0	1	0	0	0.8824
STOMACH, NONGL	M-SQUAMOUS CELL CARCINOMA	0	0	1	0	0.4937
SUBCUTANEOUS TIS	B-LIPOMA	0	1	0	0	0.5000
	M-FIBROSARCOMA	0	1	0	0	0.6667
THYROID	B-"C" CELL ADENOMA	5	6	5	5	0.5639
	B-FOLLICULAR CELL ADENOMA	1	0	0	0	1.0000
	M-"C" CELL CARCINOMA	1	0	0	1	0.4612
	M-FOLLICULAR CELL CARCINO	2	0	1	0	0.9345
UTERUS	B-ENDOMETRIAL STROMAL POL	0	1	1	1	0.3026
	M-CARCINOMA	0	1	0	0	0.7510
	M-ENDOMETRIAL STROMAL SAR	0	0	0	1	0.2451
VAGINA	B-GRANULAR CELL TUMOR	0	1	1	1	0.3026
	B-STROMAL POLYP	0	0	0	1	0.3273

Table 4A: Pairwise Comparisons of Treated Groups with Control
Male Rat - Treated Over 95 Weeks

Organ	Tumor	Cont. vs 500mg	Cont. vs 1000mg	Cont. vs 2000mg
ADRENAL, CORTEX	B-ADENOMA	1.0000	1.0000	1.0000
	M-CARCINOMA	0.4870	.	.
ADRENAL, MEDULLA	B-PHEOCHROMOCYTOMA	0.8346	0.3341	0.3488
	M-MALIGNANT PHEOCHROMOCYT	1.0000	0.5401	1.0000
BRAIN	M-ASTROCYTOMA	0.3810	.	0.4583
CAVITY, ABDOM	M-CARCINOMA (ENDOCRINE)	0.6667	.	.
	M-MESOTHELIOMA	.	0.5000	.
CORD, THORACIC	M-OLIGODENDROGLIOMA	1.0000	0.7245	1.0000
HEART	M-ENDOCARDIAL SCHWANNOMA	1.0000	1.0000	1.0000
	M-MESOTHELIOMA	.	0.5714	.
HEMATO NEOPLASIA	M-LEUKEMIA, GRANULOCYTIC	0.2516	.	.
	M-LYMPHOMA	0.3810	.	0.4486
	M-SARCOMA, HISTIOCYTIC	1.0000	0.4420	1.0000
KIDNEY	B-LIPOMA	0.3810	0.4091	0.4583
	M-HEMANGIOSARCOMA	.	0.5455	.
	M-LIPOSARCOMA	.	.	0.4583
LIVER	B-ADENOMA, HEPATOCELLULAR	1.0000	0.8037	0.8670
	M-CARCINOMA, HEPATOCELLUL	1.0000	1.0000	1.0000
LN, MESENTERIC	M-HEMANGIOSARCOMA	1.0000	0.5858	0.8497
NERVE, SCIATIC	M-SCHWANNOMA	1.0000	1.0000	1.0000
PANCREAS	B-ADENOMA, ACINAR CELL	0.0813	.	0.0290
	B-ADENOMA, ISLET CELL	0.9056	0.5723	0.4689
	M-CARCINOMA, ISLET CELL	0.3810	0.4091	0.4583
PITUITARY	B-ADENOMA	0.6995	0.8007	0.9021
	M-CARCINOMA	0.4839	.	.
PROSTATE	M-CARCINOMA	.	0.4957	.
SALIV GL, MANDIB	M-SCHWANNOMA	0.3810	.	.
SKIN, OTHER	B-HEMANGIOMA	0.4667	.	.
	B-KERATOACANTHOMA	0.9378	0.9378	0.9482
	B-SQUAMOUS CELL PAPILLOMA	1.0000	0.9125	1.0000
SKIN, OTHER	M-NEUROFIBROSARCOMA	0.3429	.	.
	M-OSTEOGENIC SARCOMA	0.3429	.	.
SPLEEN	M-UNDIFFERENTIATED STROMA	1.0000	1.0000	1.0000
SUBCUTANEOUS TIS	B-FIBROMA	0.3714	0.7857	0.3333
	B-LIPOMA	0.4286	0.5000	.
	M-FIBROSARCOMA	0.5000	0.3000	.
	M-MALIGNANT SCHWANNOMA	1.0000	1.0000	.
	M-MYXOSARCOMA	.	.	0.2000
TESTIS	B-INTERSTITIAL CELL TUMOR	0.4887	1.0000	0.7875
THYROID	B-"C" CELL ADENOMA	0.4193	0.5022	0.6640
	B-FOLLICULAR CELL ADENOMA	0.7421	0.4444	0.7500
	M-"C" CELL CARCINOMA	1.0000	0.7273	0.5357
	M-FOLLICULAR CELL CARCINO	1.0000	0.9558	1.0000
TONGUE	M-SQUAMOUS CELL CARCINOMA	.	0.4545	.
URINARY BLADDER	B-TRANSITNL. CELL PAPILLO	.	.	0.5238
	M-TRANSITNL. CELL CARCINO	0.3297	.	0.4583

Table 4B: Pairwise Comparisons of Treated Groups with Control
Female Rat - Treated Over 95 Weeks

Organ	Tumor	Cont. vs 500mg	Cont. vs 1000mg	Cont. vs 2000mg
ADRENAL, CORTEX	B-ADENOMA	0.4491	0.7083	0.7237
ADRENAL, MEDULLA	B-PHEOCHROMOCYTOMA	0.1436	0.7674	0.0408
BRAIN	B-GRANULAR CELL TUMOR	.	.	0.5000
	M-ASTROCYTOMA	0.4752	0.5000	0.4359
CERVIX	B-GRANULAR CELL TUMOR	0.7038	1.0000	0.4410
	B-POLYP,ENDOMETRIAL STROM	1.0000	1.0000	0.7237
	M-SARCOMA,ENDOMETRIAL STR	.	.	0.4914
HEART	M-ENDOCARDIAL SCHWANNOMA	1.0000	1.0000	1.0000
HEMATO NEOPLASIA	M-LYMPHOMA	0.4815	0.3750	0.2571
	M-SARCOMA, HISTIOCYTIC	0.4746	1.0000	1.0000
KIDNEY	B-ADENOMA, TUBULAR CELL	.	0.5000	.
	B-LIPOMA	0.4500	.	.
	M-LIPOSARCOMA	.	0.5000	.
	M-MALIGNANT MESENCHYMOMA	1.0000	1.0000	1.0000
LIVER	B-ADENOMA, HEPATOCELLULAR	.	.	0.5000
	M-CARCINOMA, HEPATOCELLUL	0.4500	.	.
LN, MESENTERIC	M-HEMANGIOSARCOMA	1.0000	0.6703	0.7532
MAMMARY, FEMALE	B-FIBROADENOMA	0.0914	0.3007	0.0762
	B-FIBROMA	1.0000	1.0000	1.0000
	M-CARCINOMA	0.5011	0.9312	0.8561
	M-FIBROSARCOMA	1.0000	1.0000	1.0000
OVARY	B-LUTEOMA	1.0000	1.0000	1.0000
	M-GRANULOSA/THECA CELL TU	1.0000	0.7151	0.7582
PANCREAS	B-ADENOMA, ACINAR CELL	.	0.5000	.
	B-ADENOMA, ISLET CELL	0.7778	0.2442	.
PITUITARY	B-ADENOMA	0.7165	0.7017	0.1533
	M-CARCINOMA	1.0000	0.8810	0.8441
SKIN, OTHER	M-NEUROFIBROSARCOMA	0.2143	.	.
SPLEEN	M-UNDIFFERENTIATED STROMA	0.7778	.	.
STOMACH, NONGL	M-SQUAMOUS CELL CARCINOMA	.	0.5000	.
SUBCUTANEOUS TIS	B-LIPOMA	0.5000	.	.
	M-FIBROSARCOMA	0.6667	.	.
THYROID	B-"C" CELL ADENOMA	0.5527	0.6497	0.6203
	B-FOLLICULAR CELL ADENOMA	1.0000	1.0000	1.0000
	M-"C" CELL CARCINOMA	1.0000	1.0000	0.6883
	M-FOLLICULAR CELL CARCINO	1.0000	0.8542	1.0000
UTERUS	B-ENDOMETRIAL STROMAL POL	0.4815	0.7500	0.5102
	M-CARCINOMA	0.5000	.	.
	M-ENDOMETRIAL STROMAL SAR	.	.	0.4854
VAGINA	B-GRANULAR CELL TUMOR	0.4815	0.7500	0.5102
	B-STROMAL POLYP	.	.	0.5625

Table 5A: Intercurrent Mortality Rate in Male Mice

	Control		500 mg/kg/day		1000 mg/kg/day		2000 mg/kg/day		Pos. Control	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %	No. of	Cum %
0 - 26	1	4.0	0	0	0	0	2	8.0	18	72.0
Term. Sac.	24	96.0	25	100.0	25	100.0	23	92.0	7	28.0

Table 5B: Intercurrent Mortality Rate Female Mice

	Control		500 mg/kg/day		1000 mg/kg/day		2000 mg/kg/day		Pos. Control	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %	No. of	Cum %
0 - 26	4	16.0	0	0	2	8.0	2	8.0	15	60.0
Term. Sac.	21	84.0	25	100.0	23	92.0	23	92.0	10	40.0

Table 6A: Intercurrent Mortality Comparison for Control, Low, Medium, and High Dose Groups Male Mice

Method	Test	P-value Excluding the Positive Control	P-value Including the Positive Control
Log-Rank	Homogeneity	0.2814	<0.0001
Wilcoxon	Homogeneity	0.2782	<0.0001

Table 6B: Intercurrent Mortality Comparison for Control, Low, Medium, and High Dose Groups Female Mice

Method	Test	P-value Excluding the Positive Control	P-value Including the Positive Control
Log-Rank	Homogeneity	0.2477	<0.0001
Wilcoxon	Homogeneity	0.2690	<0.0001

Table 7A: Tumor Rates and Dose Response p-values of Tested Tumors Male Mice Treated Over 26 Weeks

Organ	Tumor	Control	500mg	1000mg	2000mg	P-value
HARDERIAN GLS	ADENOMA	1/24	0/25	0/25	0/25	0.9095
LIVER	ADENOMA	0/25	0/25	0/25	1/25	0.0908
LUNGS	A/B ADENOMA	0/25	0/25	0/25	1/24	0.0908
LUNGS	CARCINOMA	1/25	0/25	0/25	0/25	0.9095
RE SYSTEM	LYMPHOSARCOMA	0/25	0/25	0/25	1/25	0.0908
SKIN, GROSS	PAPILLOMA	1/25	0/25	0/25	0/25	0.9095
SPLEEN	HEMANGIOSARCOMA	1/24	0/25	1/25	1/24	0.3918
STOMACH	PAPILLOMA	0/25	0/25	0/25	1/24	0.0908

Table 7B: Tumor Rates and Dose Response p-values of Tested Tumors Female Treated Over 26 Weeks

Organ	Tumor	Control	500mg	1000mg	2000mg	P-value
KIDNEYS	HEMANGIOMA	1/24	0/25	0/25	0/25	0.9061
LUNGS	ADENOMA	0/25	0/25	1/25	0/25	0.3223
SPLEEN	HEMANGIOSARCOMA	1/24	1/25	1/25	1/25	0.4911
UTERUS	SARCOMA	1/25	0/25	0/25	0/25	0.9061

Table 8A: Pairwise comparisons Control vs. Treated Group Mice Treated Over 26 Weeks

	P-value Control Vs.			
Tumor	Low	Medium	High	Pos. Cont.
HARDERIANGLS/ADENO	1.0000	1.0000	1.0000	1.0000
LIVER/ADENOMA	.	.	0.5098	.
LUNGS/A/BADENOMA	.	.	0.5000	0.2549
LUNGS/CARCINOMA	1.0000	1.0000	1.0000	1.0000
RESYSTEM/LYMPHOSAR	.	.	0.5098	49E-05
SKIN_GROSS/PAPILLO	1.0000	1.0000	1.0000	0.0511
SPLEEN/HEMANGIOSAR	1.0000	0.7647	0.7551	0.7647
STOMACH/PAPILLOMA	.	.	0.5000	76E-05

Table 8B: Pairwise comparisons Control vs. Treated Group Female Mice Treated Over 26 Weeks

	P-value Control Vs.			
Tumor	Low	Medium	High	Pos. Cont.
HARDERIANGLS/ADENO				0.1398
KIDNEYS/HEMANGIOMA	1.0000	1.0000	1.0000	1.0000
LUNGS/A/BADENOMA	.	.	.	0.0751
LUNGS/ADENOMA	.	0.5098	.	.
RESYSTEM/LYMPHOSAR	.	.	.	0.0014
SKIN_GROSS/PAPILLO	.	.	.	0.0227
SPLEEN/HEMANGIOSAR	0.7647	0.7647	0.7647	0.7647
STOMACH/PAPILLOMA	.	.	.	70E-05
UTERUS/SARCOMA	1.0000	1.0000	1.0000	1.0000

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

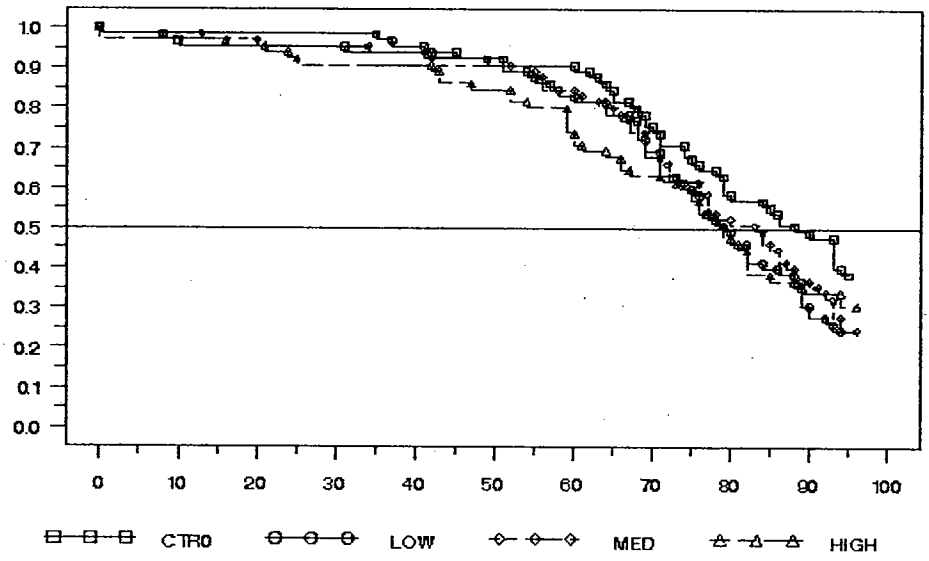


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

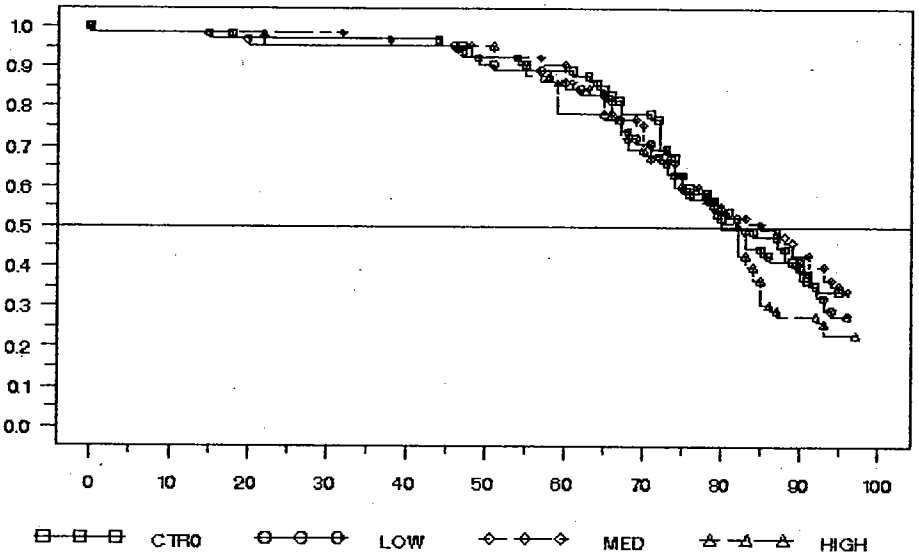


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

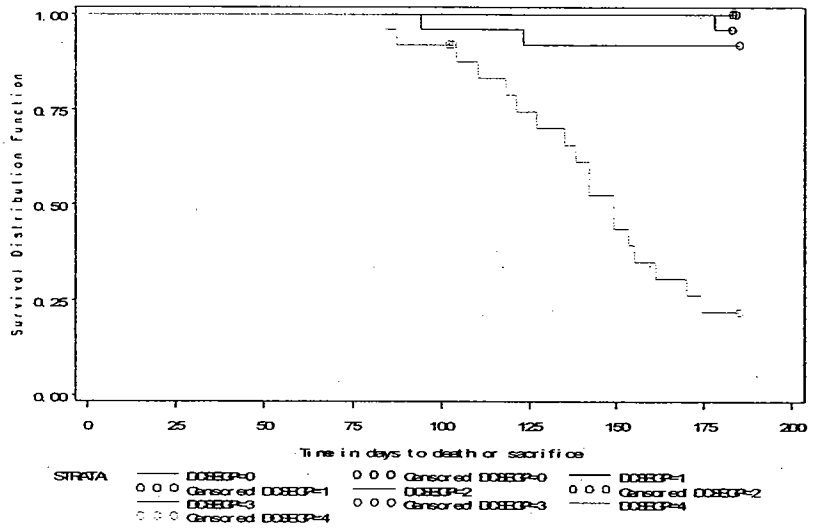
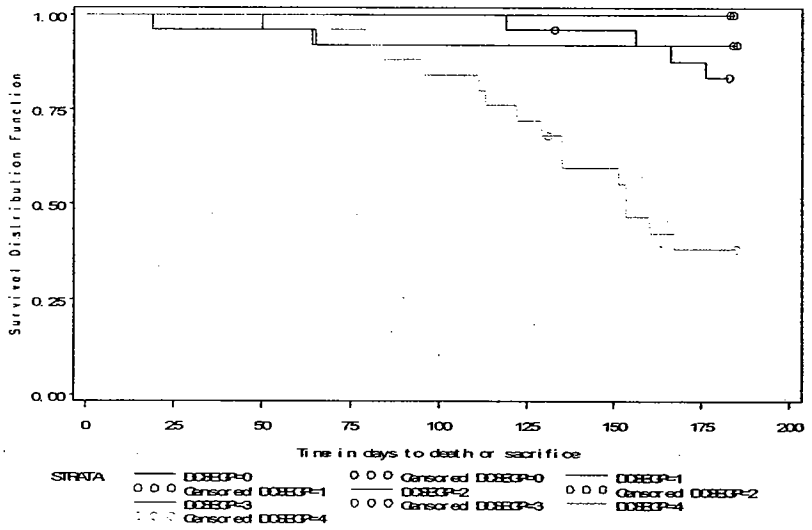


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-011 / N-000
Drug Name:	Tyzeka™ (telbivudine, LdT) 600 mg Tablets
Indication(s):	Treatment of Hepatitis B (HBV)
Applicant:	Idenix Pharmaceuticals, Incorporated
Dates:	Submitted: December 30, 2005 Received: December 30, 2005 Draft Review Completed: September 6, 2006 Final Review Completed: October 24, 2006
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics IV
Statistics Reviewer:	Fraser Smith, Ph.D., Senior Statistical Reviewer
Concurring Reviewers:	Greg Soon, Ph.D., Statistics Team Leader
Medical Division:	Division of Antiviral Products
Clinical Team:	Charlene Brown, M.D., M.P.H., Medical Reviewer Katherine Laessig, M.D., Medical Team Leader
Project Manager:	Kenny Shade, J.D., B.S.N., Regulatory Project Manager

Keywords: Compensated Chronic Hepatitis B, Therapeutic Response, Histologic Response, Serum HBV DNA, ALT Normalization, HBeAg, Ishak Fibrosis, ALT Flares, Creatine Kinase Elevations

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

There was one pivotal double-blind, randomized, controlled phase III clinical study included in this application to support the use of telbivudine (LdT) to treat adults with compensated chronic hepatitis B.

The non-inferiority of telbivudine to lamivudine was established in both HBeAg subpopulations for Therapeutic Response (the primary endpoint), Histologic Response, (the primary secondary endpoint), Serum HBV DNA Reduction, Serum HBV DNA Undetectable, ALT Normalization and Virologic Breakthrough at Week 48.

Non-inferiority of telbivudine to lamivudine was also demonstrated in the HBeAg-positive subpopulation for Virologic Response, HBeAg seroconversion and HBeAg Loss and in the HBeAg-negative subpopulation for Change in Ishak Fibrosis Score.

According to the statistical testing procedure pre-specified in the statistical analysis plan, the superiority of telbivudine over lamivudine was also demonstrated in the HBeAg-positive subpopulation for the Therapeutic Response, Histologic Response, Serum HBV DNA Reduction and Serum HBV DNA Undetectable. However since superiority for the same endpoints was not demonstrated in the HBeAg-negative subpopulation, the Division of Antiviral Products (DAVP) will require replication of the superiority findings in the HBeAg-positive subgroup in another study before allowing Idenix to make this claim in the label.

Change in Ishak Fibrosis Score for telbivudine did not meet the pre-specified non-inferioritiy criterion for the HBeAg-positive subpopulation and the p-value for the difference between telbivudine and lamivudine was almost statistically significant in favor of lamivudine.

Creatine kinase (CK) elevations were more frequent among subjects on telbivudine treatment. Grade 3/4 CK elevations occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients. Most CK elevations were asymptomatic but the recovery time was longer for subjects on telbivudine than subjects on lamivudine.

1.2 Brief Overview of Clinical Studies

NV-02B-007 was a single randomized, double-blind Phase 3 study of treatment with LdT vs. lamivudine in adults with chronic hepatitis B. All subjects were to be HbeAg positive or HbeAg negative during screening.

Eligible patients with chronic hepatitis B were to be randomly assigned (1:1) to one of the following two treatment groups:

L-dT (600 mg) + lamivudine placebo po daily × 104 weeks; OR
L-dT placebo + lamivudine 100 mg po daily × 104 weeks;

A new composite efficacy endpoint was proposed as the primary "therapeutic response." This is defined as:

Loss of detectable serum HbeAg **OR** ALT normalization
AND
Serum HBV DNA $< 10^5$ copies/ml by the COBAS Amplicor™ PCR assay.

Patients were to be pre-stratified by HbeAg status (positive or negative) at screening. The principal treatment comparisons for the primary efficacy endpoint were after one and two years of treatment.

The primary objective of this study was to determine whether LdT treatment (at 600 mg/day) produced a comparable or superior therapeutic response compared to lamivudine in adults with chronic hepatitis B.

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1.3 Statistical Issues and Findings

Clinical and virologic efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative subject populations in Study 007.

Histological Improvement and Change in Ishak Fibrosis Score at Week 52 (007 GLOBE Study)

	HBeAg-positive (n =797)		HBeAg-negative (n =417)	
	Telbivudine 600 mg (n=399)[1]	Lamivudine 100 mg (n=398)[1]	Telbivudine 600 mg (n=205)[1]	Lamivudine 100 mg (n=212)[1]
Histologic Response [2]				
Improvement	69%	60%	69%	68%
No Improvement	19%	26%	23%	25%
Missing Week 52 Biopsy	12%	15%	8%	7%
Ishak Fibrosis Score[3]				
Improvement	41%	46%	48%	44%
No Change	39%	32%	34%	43%
Worsening	9%	7%	10%	5%
Missing Week 52 Biopsy	12%	15%	8%	7%

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥ 2

[2] Histologic Response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score

[3] For Ishak Fibrosis Score, improvement defined as a ≥ 1-point reduction in Ishak fibrosis score from Baseline to Week 52

Source: Table 2 from the Telbivudine label

Compared to lamivudine patients, a significantly greater proportion of telbivudine patients in the HBeAg-positive subpopulation experienced a histologic response at Week 52. Non-inferiority was demonstrated for telbivudine in the HBeAg-negative population.

Change in Ishak Fibrosis Score for telbivudine did not meet the pre-specified non-inferioritiy criterion (lower limit of the 95% confidence interval > -8%) for HBeAg-positive patients. In

addition, the p-value for the difference between telbivudine and lamivudine in the HBeAg-positive subpopulation was almost statistically significant in favor of lamivudine. There was no statistically significant treatment difference in the HBeAg-negative subpopulation.

The primary efficacy endpoint for the phase III study was the proportion of randomized patients with a Therapeutic Response which was defined as:

- Serum HBV DNA suppression < 5 $\log_{10}$ copies/mL at Week 52

AND

- HbeAg loss at Week 52 or ALT normalized at Week 52

HBeAg loss at Week 52 was defined as loss of detectable serum HBeAg at Week 52 in a patient who was HBeAg+ at Baseline

ALT normalized at Week 52 was defined as ALT within normal limits at Week 52 for a patient with an elevated Alt level (> 1.0 × ULN) at either Baseline or Screening

Compared to lamivudine patients, a significantly greater proportion of telbivudine patients in the HBeAg-positive subpopulation experienced a therapeutic response; 67% of the lamivudine subjects and 75% of the telbivudine subjects had a therapeutic response at Week 52 in the ITT population.

Non-inferiority was demonstrated for telbivudine in the HBeAg-negative population where 77% of the lamivudine subjects and 75% of the telbivudine subjects had a therapeutic response at Week 52 in the ITT population.

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Corrections to the applicant's conclusions are noted in the table below summarizing hierarchical fixed hypothesis testing results for primary and secondary endpoints in study NV-02B-007.

Results of hierarchical fixed hypothesis testing of primary and secondary efficacy endpoints

Efficacy Endpoint*		Subpopulations	
		HBeAg-positive	HBeAg-negative
1	Therapeutic Response	S	NI
2.1	Histologic Response	S	NI
2.2	Serum HBV DNA Reduction	S	~~S~~[1] NI
2.3	Serum HBV DNA Undetectable	S	~~S~~[1] NI
2.4	ALT Normalization	NI	NI
2.5	Virologic Breakthrough at Week 48	~~S~~[1] NI	~~S~~[1] NI
2.6	Virologic Response	NI	/
2.7	HBeAg Seroconversion	NI	/
2.8	HBeAg Loss	NI	/
2.9	Change in Ishak Fibrosis Score	~~NI~~[2]	NI
2.10	Primary Treatment Failure	~~S~~[1]	Unable to achieve superiority
2.11	HBsAg Loss	~~NI~~[3]	/
2.12	HBsAg Seroconversion	~~NI~~[3]	/

Source: Table 11-20 in the Clinical Study Report
*All Endpoints are for Week 52 unless otherwise specified.
Note: S = Superiority
NI = Non-Inferiority
/ = Not Applicable.
[1] Superiority for the current test (e.g., 2.5) cannot be demonstrated because previous test (e.g., 2.4) did not demonstrate superiority
[2] Failed to demonstrate non-inferiority (see Table 11-28)
[3] Only a small percentage had HBsAg loss of in the first year of treatment and the statistical analysis plan stated that there would be no non-inferiority test for this endpoint.

Based on our review of the collective data we conclude the following.

1. LdT was superior to lamivudine in the HBeAg-positive subpopulation and non-inferior to lamivudine in the HBeAg-negative subpopulation for the following endpoints: Therapeutic Response (primary endpoint), Histologic Response (Key Secondary Endpoint), Serum HBV DNA Reduction, and Serum HBV DNA Undetectable.

2. LdT was non-inferior to lamivudine in both HBeAg subpopulations for ALT Normalization and Virologic Breakthrough at Week 48. .

3. LdT was also non-inferior to lamivudine in the HBeAg-positive subpopulation for Virologic Response, HBeAg Seroconversion and HBeAg Loss.

4. The study failed to demonstrate that LdT was non-inferiority to lamivudine for change in Ishak Fibrosis Score in the HBeAg-positive subpopulation and the treatment difference was almost statistically significant in favor of lamivudine.

The applicant cannot claim superiority for any secondary endpoints in the hierarchy if LdT was not superior to lamivudine for any previous endpoints. For example, in the HBeAg-negative subpopulation, LdT is not superior to lamivudine for Serum HBV DNA Reduction or Serum HBV DNA Undetectable because LdT was not superior to lamivudine for the therapeutic response or the histologic response endpoints. Corrections by the statistical reviewer are indicated by crossing a line through the applicant's claim of NI or S and providing reasons in footnotes.

In the HBeAg-positive subpopulation, since Virologic Breakthrough at Week 48 and Primary Treatment Failure were after ALT Normalization in the hierarchy of fixed hypothesis testing, and telbivudine was not shown to be superior to lamivudine with respect to ALT normalization, it is not valid to claim that telbivudine is superior to lamivudine for Virologic Breakthrough or Primary Treatment Failure.

Non-inferiority of telbivudine to lamivudine can be claimed for Virologic Breakthrough at Week 48 in the HBeAg-positive subpopulation even though a non-inferiority margin was not pre-specified because there was a statistically significant difference in favor of LdT for this endpoint (i.e., the lower bound of the confidence interval was greater than 0, the smallest possible non-inferiority margin).

Non-inferiority of telbivudine to lamivudine cannot be claimed for Primary Treatment Failure in the HBeAg-positive subpopulation because non-inferiority for Change in Ishak Fibrosis Score was not achieved previously in the hierarchical testing procedure. There was no statistically significant difference between telbivudine and lamivudine for primary treatment failure in the HBeAg-negative subpopulation.

However in the statistical review we will determine whether LdT is superior to lamivudine for a given endpoint in study NV-02B-007 only based upon the hierarchical fixed hypotheses that were pre-specified in the SAP.

Compared to lamivudine, the percentage of patients with new CK elevations with toxicity grade ≥ 1 was significantly higher in telbivudine patients; 488/680 (72%) of telbivudine patients had new CK elevations with toxicity grade ≥ 1 compared to only 285/687 (41%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

Compared to lamivudine, the percentage of patients whose worst CK toxicity grade was 1 or 2 during the period was significantly higher in telbivudine patients; 427/680 (63%) of telbivudine patients had new grade 1/2 CK elevations compared to only 263/687 (38%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

Compared to lamivudine, the percentage of patients with new grade 3/4 CK elevations was significantly higher in telbivudine patients; 61/680 (9%) of telbivudine patients had new grade 3/4 CK elevations compared to only 22/687 (3%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

***NV-02B-007*: Summary of Number (and percentage) of patients with CK elevations On Treatment who recovered on or off treatment**

Toxicity Grade	Treatment	Number (%) of CK Elevations	Number (%) who Recovered	Mean Recovery Time (Days)[1]	Median Recovery Time (Days)[1]
1-4	LdT	488/680=72%	208/488=43%	183	131
	Lamivudine	285/687=41%	208/285=73%	164	64
1-2[2]	LdT	427/680=63%	191/427=45%	174	106
	Lamivudine	263/687=38%	199/263=76%	156	63
3-4	LdT	61/680=9%	51/61=84%	58	36
	Lamivudine	22/687=3%	20/22=91%	46	29

Source: Statistical Reviewer's Analysis
[1] Mean and Median Recovery Time computed for patients who recovered from CK elevations
[2] Only patients whose worst laboratory toxicity grade is 1 or 2 during the period are included

The percentage of patients with CK elevations who recovered and corresponding time to recovery among patients who recovered were also summarized by the statistical reviewer. Recovery was defined as a final CK measurement below the upper limit of normal or below the given toxicity grade. Time to recovery was defined as the time it took after a CK elevation to observe the first CK measurement and all subsequent CK measurements to be below the upper limit of normal or below the given toxicity grade.

On page 182 of the clinical study report, the applicant claimed that CK elevations were brief and didn't require treatment discontinuation. However, compared to lamivudine, a smaller percentage of patients randomized to LdT recovered from CK elevations and recovery from CK elevations took longer in LdT patients.

2. INTRODUCTION

2.1 Overview

NV-02B-007 was a single randomized, double-blind Phase 3 study of treatment with LdT vs. lamivudine in adults with chronic hepatitis B. All subjects were to be HbeAg-positive or HbeAg-negative during screening.

Eligible patients with chronic hepatitis B were to be randomly assigned (1:1) to one of the following two treatment groups:

L-dT (600 mg) + lamivudine placebo po daily × 104 weeks; OR
L-dT placebo + lamivudine 100 mg po daily × 104 weeks;

A new composite efficacy endpoint was proposed as the primary "therapeutic response." This is defined as:

Loss of detectable serum HbeAg **OR** ALT normalization
AND
Serum HBV DNA < 10^5 copies/ml by the COBAS Amplicor™ PCR assay.

Patients were to be pre-stratified by HbeAg status (positive or negative) at screening. The principal treatment comparisons for the primary efficacy endpoint were after one and two years of treatment.

The primary objective of this study was to determine whether LdT treatment (at 600 mg/day) produced a comparable or superior therapeutic response compared to lamivudine in adults with chronic hepatitis B.

2.2 Data Sources

This statistical review is based on data submitted for Study NV-02B-007.

The electronic submission of the NDA can be found in the FDA, Center for Drug Evaluation and Research (CDER) internal network directory of

\\Cdsesub1\evsprod\nda022011\0000.

SAS programs and SAS datasets provided by the company can be found in

\\Cdsesub1\evsprod\nda022011\0000\m5\datasets\nv02b007.

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Two-stage statistical testing was performed for this protocol. The first one was a test for non-inferiority relative to the lamivudine arm. If non-inferiority was asserted, then a test for superiority was performed. No multiplicity adjustments were necessary.

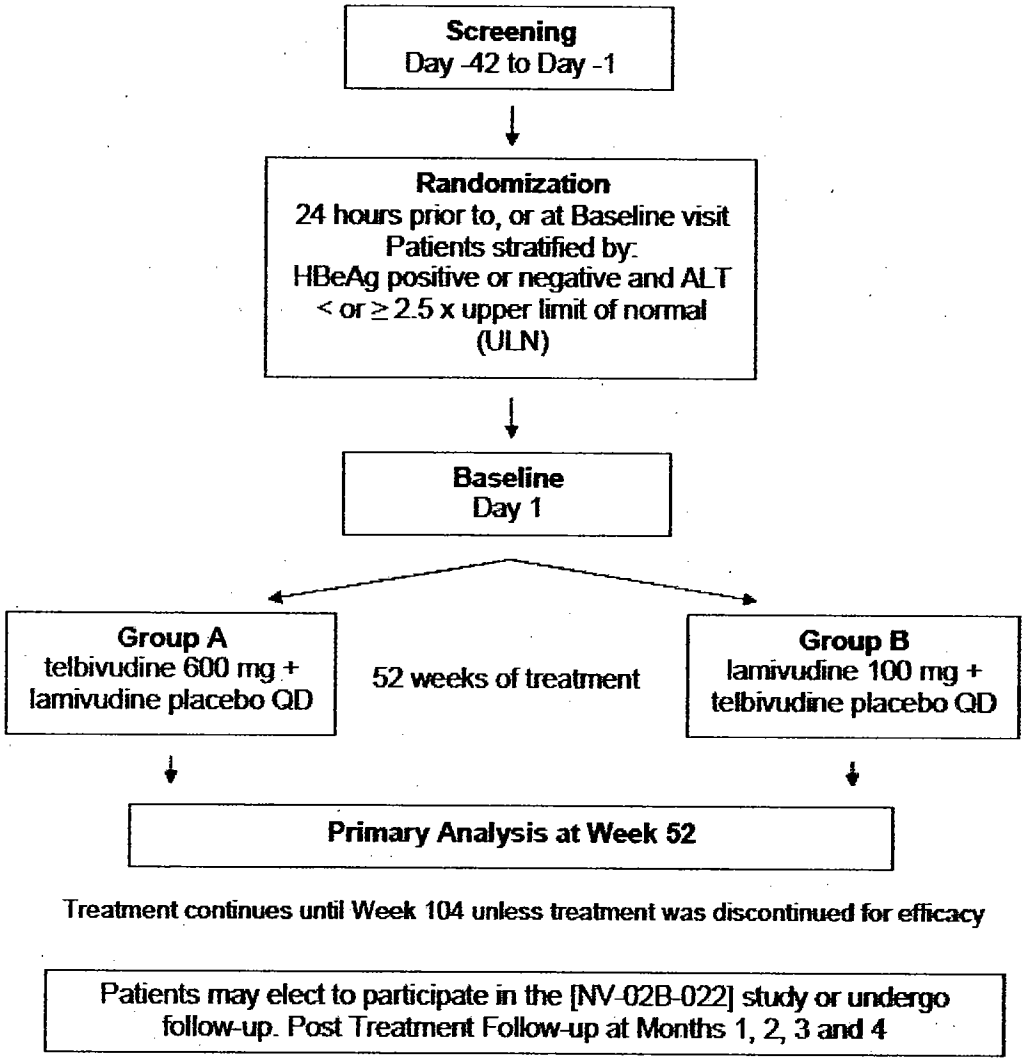
The primary endpoint included HbeAG loss OR ALT normalization for the HbeAg-positive subgroup and only ALT normalization for the HbeAg-negative subgroup. In addition, serum HBV DNA suppression had to be $<10^5$ copies / ml (determined by quantitative PCR assay) for both subgroups.

The applicant stated that the most important secondary efficacy parameter for the HbeAg-positive subgroup was complete virologic response, defined as HbeAg loss with HBV DNA$<10^5$ copies/ml.

For the HbeAg-negative subgroup, the applicant stated that the most important secondary efficacy endpoint was "serologic response", comprising serum ALT normalization and HBV DNA response (defined as suppression of serum HBV DNA to $<10^5$ copies/ml). This endpoint was analogous to a combined biochemical plus virologic response endpoint used in several previous trials of HBV therapeutics in HbeAg-negative patients.

3.1.1 Study Design

Figure 9-1 Study design - NV-02B-007



Source: Figure 9-1 in the Clinical Study Report

3.1.2 Methods for Statistical Analysis of Efficacy Data

The primary efficacy endpoint was the proportion of randomized patients with a therapeutic response (defined above in the Overview Section).

The sponsor committed to 400 subjects/arm/protocol. Sample size calculations were performed in order to obtain 80% power with a 0.00125 significance level using a 15% non-inferiority criterion assuming a response rate of 50% in the lamivudine arm.

The applicant stated that traditionally, the non-inferiority margin has been calculated to be half the distance between response rates of the active control arm vs. placebo based on literature data. With the proposed composite primary efficacy endpoint, there were no precisely analogous historical data. The applicant's best estimations of response rates for the therapeutic response were 50% for lamivudine and 10% for placebo treated patients. Half of the distance of the lamivudine effect over placebo is 20%. Therefore they conservatively proposed a difference of 15% as the minimum criterion for non-inferiority.

Justification of non-inferiority margins for other secondary endpoints is given in Section 4.4 the statistical analysis plan (IND 60459, Serial Number 168, finalized on June 13, 2005).

For the primary efficacy analysis, the confidence interval with a pre-specified significance level for the difference in therapeutic response rates between LdT and lamivudine was estimated. If the lower boundary of the confidence interval was above –15%, non-inferiority was claimed, and if the lower boundary is at or above 0%, superiority was claimed.

For data analysis purposes, patients were to be pre-stratified by HbeAg status (positive or negative) at screening. For the purposes of adequately assessing HbeAg responses in the HbeAg-positive subgroup, enrollment in the HbeAg-positive stratum was to be at least 45% of the total study population (i.e., at least 360 patients).

A 3-step statistical test procedure described in Lu and Huque [Biometrical Journal 43 (2001) 7, 909-923] was utilized for the primary endpoint analyses to control the Type I error rate in the analysis of the two HBeAg subpopulations and the Overall population. This 3-step procedure was also applied to the key secondary endpoint, Histologic Response. The method is summarized below.

1. A separate statistical analysis was performed initially for both HBeAg+ and HBeAg- subpopulations utilizing an α-level of 0.0432. If both subpopulations showed statistical significance, the primary statistical analysis for the overall patient population was considered to be statistically significant.

2. If statistical significance was not established within both the HBeAg+ and HBeAg- subpopulations, a statistical test of treatment group interactions between the two HBeAg subpopulations was performed. A significant interaction test was defined using the α-level of 0.15.

3. If there was no significant treatment interaction between the two patient subpopulations, a pooled statistical analysis for the overall patient population was performed using an α-level at 0.000933. If this overall test was statistically significant, the primary statistical analysis for the overall patient population was considered to be statistically significant.

Using this procedure, the overall Type I error rate for the primary endpoint was controlled at the 0.00125 level (for a two-sided test).

The **Intent-to-Treat (ITT)** population was defined as all randomized subjects who presumptively received at least one dose of study medication with at least one observation after baseline. Patients who received the wrong study medication were to be analyzed according to the group to which they were randomized. Patients who had treatment discontinued for efficacy were to have post-treatment endpoint values summarized separately.

The use of concomitant medications was to be tabulated using WHO drug classifications and summarized by treatment group. Any patient who received other anti-HBV medications while study medication was to be included in the ITT analyses, but the data were to be censored on the day they first took the prohibited medication.

The **Efficacy-evaluable (EE)** population included all randomized patients who presumptively received at least one dose of study drug and who did not exhibit major protocol violations with regard to key entry criteria. Patients in the EE population met the following criteria:

- Documented chronic hepatitis B, including a detectable HBsAg level at Screening
- ALT $\geq 1.0 \times$ ULN at either the Screening or Baseline visit (or both)
- Screening serum HBV DNA level ≥ 6 $\log_{10}$ copies/mL
- No HCV, HDV, HIV-1, or HIV-2 co-infection
- No prior lamivudine or investigational anti-HBV nucleoside or nucleotide analogue at any time
- No medical condition that required prolonged or frequent use of systematic acyclovir or famciclovir (e.lg., for recurrent herpes virus infections)
- No known primary or secondary causes of liver disease other than hepatitis B

Patients who were assessed with poor treatment compliance, defined as <75% of study visits where the investigators assessment of treatment compliance was "Fair" or "Good", or receiving two consecutive ratings of "Poor" were to be excluded from the EE population.

In the analyses using the EE population, patients who received the wrong study medication were to be analyzed according the study medication actually received.

The primary population was prospectively defined to be the ITT population for superiority tests of efficacy endpoints. The primary population was defined to be the EE population for efficacy tests of non-inferiority. An exception is the Histologic Response endpoint which will use the modified ITT population as the primary analysis population for both superiority and non-inferiority tests.

The **Histologic Response** populations were to include all patients in the ITT population who had evaluable pretreatment liver biopsies. Patients in the ITT population meeting this criterion comprised the **modified ITT** (mITT) population for assessment of Histologic Response. Patients from the EE population meeting this criterion whose baseline liver biopsy had a Knodell HAI score >3 comprised the **modified EE** (mEE) population for assessment of Histologic Response.

The **Safety** population included all patients who presumptively received at least one dose of study medication with at least one post-baseline observation. In the safety population, patients were to be analyzed according to the treatment they received (as opposed to the treatment to which they were randomized).

When the patients met the protocol criteria for treatment discontinuation due to efficacy, any missing data thereafter were to be considered as treatment responders thereafter in the ITT and EE populations (CSR page 69).

When patients met the protocol criteria for treatment discontinuation for disease progression or lack of efficacy or for Virologic Breakthrough, any missing data thereafter were to be considered as treatment failures in the ITT and EE populations.

With the exception of the above criteria for treatment discontinuation, breakthrough, HBV resistance and treatment failure, missing categorical data were to be excluded from the EE analyses (i.e., missing = missing) and treated as no response (i.e., missing = failure) in the ITT analyses.

For the efficacy parameters of virologic breakthrough, HBV resistance and treatment failure, the LOCF method was used for missing data in both the ITT and EE analyses. For missing continuous variables, the LOCF was to be applied in the EE analysis and observations with missing data were to be set to missing in the ITT analysis.

HBV DNA assay results below the LLOQ of the assay were to be assigned a value of half of the LLOQ copies/mL or the log-transformed value of half of the LLOQ copies/mL.

According to Table 4-8 in the SAP, missing data for patients study withdrawals and intermittent missing data were to be treated as failures in the ITT Population and replaced using the LOCF in the Efficacy Evaluable Population for the following endpoints: Therapeutic Response, HBV DNA Non-Detectable, Virologic Response, HBeAg Loss, HBeAg Seroconversion, Three Component HBeAg Seroconversion, ALT Normalization, Composite Serologic Response, HBsAg loss, HBsAg Seroconversion, and HBV DNA Suppression.

According to Table 4-8 in the SAP, missing data for patients study withdrawals and intermittent missing data were to be treated as failures in the ITT and EE Populations for the following endpoints: Knodell HAI Score (and sub-scores), Histologic Response, Ishak Fibrosis Score, Change in Ishak Fibrosis Score, Composite Serologic-Histologic Efficacy.

Appears This Way
On Original

Method of Handling Missing Data for Patient Study Withdrawals and Intermittent Missing Data

<table>
<tr><th colspan="2">Endpoint</th><th>Missing Data Method</th></tr>
<tr><td>• Therapeutic Response
• HBV DNA Non-Detectable
• Virologic Response
• HBeAg Loss
• HBeAg Seroconversion
• Three Component HBeAg Seroconversion</td><td>• ALT Normalization
• Composite Serologic Response
• HBsAg loss
• HBsAg Seroconversion
• HBV DNA Suppression</td><td>ITT: Failure
EE: LOCF</td></tr>
<tr><td>• Knodell HAI Score
• Ishak Fibrosis Score
• Change in Ishak Fibrosis Score</td><td>• Histologic Response
• Composite Serologic-Histologic Efficacy</td><td>ITT: Missing
EE: Missing</td></tr>
<tr><td colspan="3">Note: As a patient will have only one post-baseline liver biopsy LOCF is not applicable</td></tr>
<tr><td>• Virologic Breakthrough</td><td>• Treatment Failure</td><td>ITT: LOCF
EE: LOCF</td></tr>
<tr><td colspan="3">Note: According to the applicant the LOCF more accurately represents these specific negative efficacy endpoints and that patients who discontinue treatment for other reasons (e.g. adverse event, non-compliance) should not be categorized as virologic breakthrough by default.</td></tr>
<tr><td>• Serum ALT</td><td>• Serum HBV DNA</td><td>ITT: Missing
EE: LOCF</td></tr>
<tr><td colspan="3">Note: Continuous variables will be set to missing in the ITT population.</td></tr>
</table>

Source: Table 4-8 from the SAP

(Note: Missing of Handling Missing Data for Treatment Discontinuation due to Efficacy was discussed in Section 4.7.1 of the SAP)

Efficacy endpoints overall and by HBeAg subpopulation

Efficacy endpoint	Population		
	Overall	HBeAg-positive	HBeAg-negative
Primary Endpoint: Therapeutic Response1	X	X	X
Key Secondary endpoint: Histologic Response	X	X	X
Serum HBV/HBV DNA Reduction	X	X	X
HBV DNA Suppression to <5 log10 copies/mL	X	X	X
PCR Non-detectable HBV DNA	X	X	X
ALT Normalization	X	X	X
HBeAg-related responses: HBeAg Loss, HBeAg Seroconversion, 3-Component HBeAg Seroconversion		X	
Virologic Response,		X	
Composite Serologic-Histologic Efficacy	X	X	X
HBsAg Loss/HBsAg Seroconversion	X	X	X
Treatment Discontinuation Due to Efficacy	X	X	X
Treatment Failure/primary and secondary	X	X	X
Virologic Breakthrough	X	X	X
Treatment-Emergent HBV Resistance	X	X	X
Post-Treatment Relapse	X	X	X

Source: Table 9-7 of the Clinical Study Report and Section 2.3.4 (Appendix 16.1.9) of the SAP
1Composite Serologic Response – also called Compositive Serologic Response when applied to HBeAg-negative patients

The primary and secondary efficacy evaluations and the populations included in each evaluation were summarized by the applicant in Table 9-7 of the Clinical Study Report.

Some endpoints were specific **to HBeAg** subpopulations. To differentiate between analyses on an entire population versus an HBeAg subpopulation, **the term "Overall" was used to describe** the total study population (e.g., Overall ITT population or Overall Safety population) which would include both HBeAg subpopulations.

There was a 21-patient discrepancy between the 921 patients randomized as HBeAg-positive using the IVRS system vs. 900 patients found to be HBeAg-positive using the screening data at the central laboratory. This discrepancy was due to the clinical investigators inadvertently assigning the wrong strata through the IVRS system at randomization.

For ITT analyses, the HBeAg subpopulation was determined based on the value used for randomization by the IVRS system while for EE analyses, the actual HBeAg result from the screening visit was used to determine the respective subpopulation.

The applicant summarized the definitions of a number of categorical efficacy endpoints in Table 9-8 of the Clinical Study Report. A full description of the definitions of the study endpoints was provided in the SAP.

Definitions of categorical efficacy of endpoints

Endpoint	Definition
Therapeutic Response	Serum HBV DNA <5 log10 copies/mL and either HBeAg loss or ALT normalization
Therapeutic Response also called Composite Serologic Response (HBeAg- negative patients only)	Serum HBV DNA <5 log10 copies/mL and ALT normalization
Histologic Response	≥2-point reduction in Knodell necroinflammatory score without a worsening in fibrosis score
HBV DNA suppression	In patients with ≥6 log10 copies/mL at Baseline, serum HBV DNA <5 log10 copies/mL on two consecutive visits or at the last visit*
PCR Non-detectable HBV DNA	HBV DNA below LLOQ (<300 copies/mL)1
ALT normalization	If ALT levels were elevated (>ULN) at Baseline, ALT within normal limits on two consecutive visits or at the last visit*
HBeAg loss (HBeAg-positive only)	Loss of detectable HBeAg if HBeAg was detected at Baseline
HBeAg seroconversion (HBeAg-positive only)	HBeAg loss; if HBeAg was defected at Baseline, with gain of detectable HBeAb
Virologic Response (HBeAg-positive patients only)	HBV DNA <5 log10 copies/mL and HBeAg loss

Endpoint	**Definition**
3-component HBeAg seroconversion (HBeAg-positive only)	HBeAg seroconversion and HBV DNA <5 log10 copies/mL
HBsAg loss	Loss of detectable HBsAg if HBsAg was detected at Baseline
HBsAg seroconversion	HBsAg loss, if HBsAg was detected at Baseline, and gain of detectable HBsAb
Virologic Breakthrough	In patients with HBV DNA levels of ≥6 log10 copies/mL at Baseline who subsequently achieved two consecutive HBV DNA values <5 log10 copies/mL, and has (1) HBV DNA ≥5 log10 copies/mL on two consecutive visits with no more than one subsequent value <5 log10 copies/mL or (2) HBV DNA ≥5 log10 copies/mL at the last treatment visit OR In patients who never achieved two consecutive HBV DNA levels <5 log10 copies/mL but achieved ≥2 log10 copies/mL reduction from Baseline, and has (1) return of HBV DNA to within 1 log10 copies/mL of Baseline on two consecutive visits, with no more than one subsequent level >1 log10 copies/mL below Baseline or (2) a single HBV DNA level within 1 log10 copies/mL of Baseline at the last treatment visit
Treatment-emergent HBV resistance	Virologic Breakthrough by Week 48 with genotypic evidence of resistance -associated mutations in HBV DNA amplified from patient sera.
Primary treatment failure	After completion of 24 weeks of treatment, HBV DNA never fell to <5 log10 copies/mL for two consecutive visits after the start of study treatment

Endpoint	Definition
Secondary treatment failure	At Week ≥24, ALT increases to 10 × ULN on ≥2 visits over ≥7 days and either serum HBV DNA is ≥6 log10 copies/mL or it meets the definition of Virologic Breakthrough OR After Week 24, serum ALT level is ≥2 × ULN for 16 weeks and serum HBV DNA is either ≥6 log10 copies/mL or HBV DNA pattern meets the definition of Virologic Breakthrough OR Study discontinuation for clinically significant hepatic disease progression as indicated on the CRF OR Study discontinuation for lack of efficacy after Week 24 as indicated on the CRF OR Study discontinuation upon patient, investigator, or Sponsor request after Week 24 and: (1) serum ALT ≥2 × ULN for the last two on-treatment visits, and (2) the last on-treatment serum HBV DNA value is ≥6 log10 copies/mL or meets the definition of Virologic Breakthrough
Treatment Discontinuation Due to Efficacy (qualifying criteria)	If HBeAg-positive at entry, completed ≥52 weeks of study drug treatment, exhibited Virologic Response, and exhibited HBeAg loss for ≥24 weeks OR If HBeAg-negative at entry, completed ≥52 weeks of study drug treatment AND had HBsAg loss documented on ≥2 consecutive study visits

Source: Table 9-8 from the Clinical Study Report
*Per Statistical Analysis Plan Addendum dated 30 June 2005. Last visit is defined as the last visit occurring prior to or on the patient's censoring date.
1See Changes in planned analyses, Section 9.8
Maintained endpoint response (for Therapeutic Response, HBV DNA, ALT normalization, HBeAg loss or seroconversion, or Virologic Response) is response documented on at least two consecutive visits and at the last treatment visit with no two intervening consecutive disqualifying values
Sustained endpoint response (for HBV DNA suppression, ALT normalization, HBeAg loss or seroconversion, or Virologic Response) is response documented on at least two consecutive visits and at the last study visit with no two intervening consecutive disqualifying values

3.1.3 Patient Disposition

Patient disposition for the primary 52-week treatment period

	Lamivudine		Telbivudine	
Patient populations	N	(%)	N	(%)
ITT & Safety populations	687	(100)	680	(100)
EE population	668	(97)	662	(97)
Reason for study discontinuation	**n**	**%**	**n**	**%**
ITT & Safety populations – any reason	32	(4.7)	18	(2.6)
Noncompliance	3	(0.4)	3	(0.4)
Pregnancy	2	(0.3)	1	(0.1)
Adverse event(s)	5	(0.7)	2	(0.3)
Clinical disease progression	2	(0.3)	0	
Lack of efficacy after Week 24	1	(0.1)	0	
Death	1	(0.1)	0	
Request*	18	(2.6)	12	(1.8)
EE population - any reason	30	(4.5)	16	(2.4)
Noncompliance	2	(0.3)	3	(0.5)
Pregnancy	2	(0.3)	1	(0.2)
Adverse event(s)	5	(0.7)	2	(0.3)
Clinical disease progression	2	(0.3)	0	
Lack of efficacy after Week 24	1	(0.1)	0	
Death	1	(0.1)	0	
Request*	17	(2.5)	10	(1.5)

Source: Table 10-2 of the Clinical Study Report
*Patient-, investigator-, or Sponsor-initiated request.

4.7% of the lamivudine patients discontinued from the study compared to only 2.6% of LdT patients. Discontinuation rates were similar or somewhat higher for lamivudine patients for each adverse event listed in Table 10-2.

Medical Officer's Table of Subject Disposition by treatment group for the first year of dosing

Disposition of Subjects	**Lamivudine** (n=687)	**Telbivudine** (n=680)
Total Treated	**687**	**680**
Subjects discontinued from Study	**44**	**46**
• Adverse Event [a, b, c, d]	7	7
• Death	1	0
• Non-Compliance [e]	3	4
• Pregnancy	2	1
• Subject, Investigator, Applicant-Initiated Request	20	13
• Clinical Disease Progression	3	0
• Lack of Efficacy after week 24	3	0
• Efficacy [f]	5	21
Subjects continued in study	**643**	**634**

Source: Table 7.1.3.1A in Medical Officers' review of the electronic listings datasets (DISC, STUDYSUZ (120 d safety update), AE), case report forms, and written submissions for NV-02B-007

[a] Subject 007-008-036 (LAM) was removed from the Subject, Investigator, Applicant Request category and recoded in the discontinuation due to an adverse event category.

[b] Subject 007-008-079 (LAM) was removed from the Subject, Investigator, Applicant Request category and recoded in the discontinuation due to an adverse event category, based on the narrative.3

[c] Subject 007-131-002 (LdT) was removed from Subject, Investigator, Applicant Request category and recoded in the discontinuation due to an adverse event category, based on the CRF report of an ongoing AE of lethargy at the time of study drug discontinuation.

[d] See Table Table 7.1.3.2 for detailed analysis of subject discontinuations due to adverse events.

[e] These results do not include the three subjects that were discontinued because they had no post-baseline observations.

[f] Source: Table 14.2.17.1 in NV-02B-007 Study Report

There were slight differences between the subject disposition described by the applicant and the medical reviewer. This Medical Reviewer recoded the reason for discontinuation for some of the subjects as per the explanation provided in the footnotes for Table 7.1.3.1A in the Medical Officer's review. Also, additional subjects with study drug discontinuations due to adverse events were found in the adverse event dataset that were not included in the applicant's overall tabulation of study drug discontinuations due to adverse events.

Other slight differences are due to the additional length of patient follow-up in the patient disposition table in the medical officer's review which is based on the data available at the time of database lock while the applicant's table was restricted to the first 52 weeks of the study. When the applicant locked the database for the primary analysis, it was determined that approximately 31% of subjects had completed the Week 68 study visit.
As noted above in Table 7.1.3.1A, the majority of subjects have continued into the second year of dosing.

Time to early study withdrawal by analysis population and treatment group, overall study data (baseline to last available visit)

	Lamivudine	Telbivudine
ITT population (N)	687	680
Early withdrawal (%)	39 (5.7)	21 (3.1)
Mean (SE), weeks	87 (0.7)	87 (0.5)
Range, weeks	2-91	2-89
EE population (N)	668	662
Early withdrawal (%)	37 (5.5)	18 (2.7)
Mean (SE), weeks	87 (0.7)	87 (0.5)
Range, weeks	2-91	2-89

Source: Table 10-3 of the Clinical Study Report
Note: The inconsistency between the mean values for the individual treatment groups and the total estimated mean is due to statistical projection.

Almost 6% of lamivudine patients withdrew early from the study compared to 3% of LdT patients (Table 10-3 of the Clinical Study Report).

Patients whose efficacy data were censored after initiation of protocol-prohibited antiviral medication up to week 52 - ITT population

Assigned treatment group	Site-patient ID number	Study day of prohibited medication initiation	Prohibited antiviral medication
Lamivudine	030-009	Day 262 (Week 37)	Adefovir dipivoxil
	080-014	Day 365 (Week 52)	Adefovir dipivoxil
	030-006	Day 396 (Week 56)*	Adefovir dipivoxil
	035-019	Day 421 (Week 60)**	Adefovir dipivoxil

Source: Table 10-5 of the Clinical Study Report
*030-006: Although the start of the prohibited med is Day 396 this data is considered a Week 52 record since the date of introduction of the medication falls between the patient's week 52 and week 60 visits; SAP
** The CRF shows that the patient's last visit is week 52. The date of prohibited med is ~6.5 weeks after the week 52 visit. Since there is no week 60 data, the med is considered week 52 record; SAP

Four lamivudine patients and no LdT patients were considered by the applicant to have taken protocol-prohibited antiviral medications between baseline and Week 52 (Table 10-5 of the Clinical Study Report).

3.1.4 Demographics and Baseline Characteristics

Demographic summary by treatment group - Overall ITT population

Parameter	Lamivudine N=687	Telbivudine N=680	p-value
Age (years)			
mean (SE)	36.2 (0.46)	35.5 (0.45)	0.2765
median	35.0	34.0	
25%, 75%	26.0, 45.0	26.0, 44.0	
range	16.0, 68.0	16.0, 68.0	
Gender, n (%)			
Male	529 (77.0)	507 (74.6)	0.2918
Female	158 (23.0)	173 (25.4)	
Race, n (%)			
Caucasian	111 (16.2)	98 (14.4)	0.6858
Asian*	515 (75.0)	525 (77.2)	
African/African/American	10 (1.5)	7 (1.0)	
Hispanic/Latino	8 (1.2)	4 (0.6)	
Middle East./Indian Subcontinent	11 (1.6)	14 (2.1)	
Other races	32 (4.7)	32 (4.7)	
Height§, (cm)			
mean (SE)	168.3 (0.32)	168.4 (0.32)	0.8575
median	169.0	169.0	
25%, 75%	162.8, 174.0	163.0, 174.0	
range	140.5, 198.0	132.1, 195.6	
Weight†, (kg)			
mean (SE)	69.4 (0.58)	67.8 (0.55)	0.0510
median	68.0	66.0	
25%, 75%	59.0, 77.0	58.0, 75.0	
range	38.0, 149.7	38.0, 126.0	

Source: Table 11-6 of the Clinical Study Report
*Includes Chinese, Korean, Thai, Japanese, Vietnamese, Filipino, Malay, and other Asian
§Values missing for 9 patients.
†Values missing for 2 patients

The distributions of age, gender, race, height and weight were similar in lamivudine and LdT patients. Approximately 75% of the patients were males, 75% of the patients were Asian and 15% were Caucasian.

Summary enrolment by country – ITT population

Country (N=20)	Sites (N=112)	Lamivudine (N=687)		Telbivudine (N=680)		Total
		HBeAg+ (N=463) n	HBeAg- (N=224) n	HBeAg+ (N=458) n	HBeAg- (N=222) n	
	N	(%)	(%)	(%)	(%)	n (%)
Australia	6	25 (5)	8 (4)	12 (3)	7 (3)	52 (4)
Canada	6	21 (5)	18 (8)	20 (4)	12 (5)	71 (5)
China	14	148 (32)	34 (15)	152 (33)	39 (18)	373 (27)
Czech Republic	4	5 (1)	4 (2)	6 (1)	7 (3)	22 (2)
France	8	8 (2)	6 (3)	10 (2)	7 (3)	31 (2)
Germany	3	14 (3)	5 (2)	11 (2)	10 (5)	40 (3)
Greece	2	2 (0)	9 (4)	1 (0)	2 (1)	14 (1)
Hong Kong	3	39 (8)	15 (7)	37 (8)	18 (8)	109 (8)
India	5	6 (1)	2 (1)	8 (2)	3 (1)	19 (1)
Italy	2	1 (0)	1 (0)	0	0	2 (0)
Korea	7	31 (7)	8 (4)	46 (10)	6 (3)	91 (7)
New Zealand	3	28 (6)	20 (9)	19 (4)	26 (12)	93 (7)
Poland	3	2 (0)	4 (2)	4 (1)	3 (1)	13 (1)
Singapore	3	11 (2)	9 (4)	16 (3)	12 (5)	48 (4)
Spain	4	2 (0)	10 (4)	3 (1)	4 (2)	19 (1)
Taiwan	4	29 (6)	27 (12)	26 (6)	32 (14)	114 (8
Thailand	5	33 (7)	16 (7)	39 (9)	11 (5)	99 (7)
Turkey	4	15 (3)	12 (5)	18 (4)	5 (2)	50 (4)
United Kingdom (UK)	3	5 (1)	3 (1)	2 (0)	4 (2)	14 (1)
United States (US)	23	38 (8)	13 (6)	28 (6)	14 (6)	93 (7)

Source: Table 10-1 of the Clinical Study Report
Percentage totals may not be equal to 100 due to rounding

The largest number of patients came from China (n=373, 27%), followed by Taiwan (n=114, 8%) and Hong Kong (n=109, 8%). There were 93 patients from the United States (7%).

The distribution of patients in lamivudine and LdT treatment groups appeared to be comparable in each country with the possible exception of Korea which had a higher percentage of LdT patients than lamivudine patients.

Baseline HBV serologic markers - HBeAg-positive ITT population

Laboratory parameter	Lamivudine (N=463)	Telbivudine (N=458)	p-value*
HBsAg, n (%)			0.3197
positive	462 (100)	458 (100)	
negative	1 (0)	0	
indeterminate	0	0	
HBsAb, n (%)			0.5297
positive	21 (5)	17 (4)	
negative	442 (95)	441 (96)	
indeterminate	0	0	
HBeAg, n (%)			0.4313
positive	442 (95)	432 (94)	
negative	21 (5)	26 (6)	
indeterminate	0	0	
HBeAb, n (%)			0.8981
positive	63 (14)	61 (13)	
negative	400 (86)	397 (87)	
indeterminate	0	0	
HBV DNA			0.8444
mean (SE), log10 copies/mL	9.53 (0.092)	9.51 (0.085)	
median	9.57	9.57	
25%, 75%	8.53, 10.19	8.71, 10.13	
min, max	3.6, 16.1	3.8, 16.0	

Source: Table 11-11 of the Clinical Study Report

*χ^2 test for categorical variables, t-test for continuous variables.

There were no significant differences in the distribution of HBV serologic markers in lamivudine and telbivudine HBeAg-positive patients.

Baseline HBV serologic markers - HBeAg-negative ITT population

Laboratory parameter	Lamivudine (N=224)	Telbivudine (N=222)	p-value*
HBsAg, n (%)			
positive	224 (100)	222 (100)	
negative	0	0	
indeterminate	0	0	
HBsAb, n (%)			0.8065
positive	8 (4)	7 (3)	
negative	216 (96)	215 (97)	
indeterminate	0	0	
HBeAg, n (%)			0.2355
positive	4 (2)	8 (4)	
negative	220 (98)	214 (96)	
indeterminate	0	0	
HBeAb, n (%)			0.3519
positive	220 (98)	215 (97)	
negative	4 (2)	7 (3)	
indeterminate	0	0	
HBV DNA			0.1189
mean (SE), log10 copies/mL	7.42 (0.102)	7.66 (0.118)	
median	7.12	7.21	
25%, 75%	6.35, 8.66	6.48, 8.96	
min, max	3.7, 12.1	3.0, 13.0	

Source: Table 11-12 of the Clinical Study Report

*χ_2 test for categorical variables, t-test for continuous variables.

There were no significant differences in the distribution of HBV serologic markers in lamivudine and telbivudine HBeAg-negative patients.

Table 11-13 Baseline HBV genotype

	Virologic Genotype									
HBeAg Status	**A**	**B**	**B/C**	**C**	**D**	**E**	**F**	**G**	**G/A**	**Unk**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HBeAg-negative										
lamivudine (n=224)	14 (6.3)	59 (26.3)	0	86 (38.4)	64 (28.6)	1 (0.4)	0	0	0	0
telbivudine (n=222)	12 (5.4)	59 (26.6)	0	89 (40.1)	57 (25.7)	2 (0.9)	1 (0.5)	1 (0.5)	0	1 (0.5)
HBeAg-positive										
lamivudine (n=463)	31 (6.7)	113 (24.4)	0	258 (55.7)	54 (11.7)	2 (0.4)	1 (0.2)	3 (0.6)	1 (0.2)	0
telbivudine (n=458)	24 (5.2)	129 (28.2)	1 (0.2)	259 (56.6)	42 (9.2)	0	1 (0.2)	2 (0.4)	0	0
Total										
lamivudine (n=687)	45 (6.6)	172 (25.0)	0	344 (50.1)	118 (17.2)	3 (0.4)	1 (0.1)	3 (0.4)	1 (0.1)	0
telbivudine (n=680)	36 (5.3)	188 (27.6)	1 (0.1)	348 (51.2)	99 (14.6)	2 (0.3)	2 (0.3)	3 (0.4)	0	1 (0.1)

Source: Table 11-13 of the Clinical Study Report
Unk = Unknown

The majority of patients were HBV geonotype C at baseline, particularly in the HBeAg-positive subgroup, followed by HBV genotypes B and D. The distribution of HBV genotypes appeared to be comparable in the two treatment groups.

Baseline liver function parameters - HBeAg-positive ITT population

Laboratory parameter	Lamivudine (N=463)	Telbivudine (N=458)	p-value*
ALT, IU/L			0.1269
mean (SE)	158.9 (6.30)	146.2 (5.36)	
median	111.0	110.5	
25%, 75%	74.0, 191.0	74.0, 181.0	
min, max	25, 1133	19, 1137	
ALT Categories (IU/L)			0.5993
<1 x ULN, n (%)	17 (4)	14 (3)	
1 x ULN to <2 x ULN, n (%)	153 (33)	149 (33)	
2 x ULN to <5 x ULN, n (%)	204 (44)	219 (48)	
≥5 x ULN, n (%)	89 (19)	76 (17)	
missing, n (%)	0	0	
mean (SE) - x ULN	3.52 (0.140)	3.27 (0.117)	0.1694
Albumin, g/dL			0.1359
mean (SE)	4.42 (0.018)	4.46 (0.018)	
median	4.40	4.45	
25%, 75%	4.20, 4.70	4.20, 4.70	
min, max	2.7, 5.9	3.2, 5.5	
Bilirubin, mg/dL			0.1751
mean (SE)	0.78 (0.016)	0.75 (0.016)	
median	0.70	0.70	
25%, 75%	0.50, 0.90	0.50, 0.90	
min, max	0.2, 2.5	0.1, 2.1	

Source: Table 11-14 of the Clinical Study Report

*χ^2 test for categorical variables, t-test for continuous variables.

Among patients who were HBeAg-positive at baseline, there were no statistically significant differences in the baseline liver function parameters between the lamivudine and LdT treatments. The same was true for the HBeAg-negative subpopulation.

Baseline liver function parameters - HBeAg-negative ITT population

Laboratory parameter	Lamivudine (N=224)	Telbivudine (N=222)	p-value*
ALT, IU/L			0.5477
mean (SE)	143.7 (8.74)	137.0 (6.94)	
median	98.5	99.0	
25%, 75%	67.5, 175.0	68.0, 169.0	
min, max	12, 982	31, 569	
ALT Categories (IU/L)			0.6157
<1 x ULN, n (%)	15 (7)	18 (8)	
1 x ULN to <2 x ULN, n (%)	84 (38)	74 (33)	
2 x ULN to <5 x ULN, n (%)	88 (39)	98 (44)	
≥5 x ULN, n (%)	37 (17)	32 (14)	
missing, n (%)	0	0	
mean (SE) - x ULN	3.14 (0.185)	2.98 (0.144)	0.5010
Albumin, g/dL			0.3365
mean (SE)	4.37 (0.024)	4.40 (0.024)	
median	4.35	4.40	
25%, 75%	4.10, 4.60	4.20, 4.60	
min, max	3.5, 5.4	3.3, 5.3	
Bilirubin, mg/dL			0.7019
mean (SE)	0.75 (0.023)	0.74 (0.025)	
median	0.70	0.70	
25%, 75%	0.50, 0.90	0.50, 0.90	
min, max	0.2, 2.2	0.2, 3.4	

Source: Table 11-15 of the Clinical Study Report

*χ^2 test for categorical variables, t-test for continuous variables.

Evaluable histology slides at Baseline – mITT population

Population	HBeAg-positive	HBeAg-negative
ITT	921	446
mITT	872 (5.3% missing)	430 (3.6% missing)
mITT with paired biopsies	753 (86.4% of mITT)	394 (91.6% of mITT)

Source: Table 11-16 of the Clinical Study Report

Approximately 4-5% of the mITT population had missing histology slides at baseline.

Mean liver histology scores at Baseline by HBeAg status - mITT population

	HBeAg-positive Lamivudine	HBeAg-positive Telbivudine	HBeAg-negative Lamivudine	HBeAg-negative Telbivudine
Histology evaluation	(n=433)	(n=439)	(n=218)	(n=212)
Knodell HAI, total or component, mean				
Total HAI score (sum of I-IV)	9.0	8.9	9.6	9.0
Necroinflammatory score (sum of I-III)	7.3	7.4	7.6	7.3
I. Periportal +/- bridging necrosis	2.8	2.8	2.9	2.8
II. Intralobular degeneration & focal necrosis	1.9	2.1	2.0	1.9
III. Portal inflammation	2.6	2.6	2.7	2.6
IV. Fibrosis	1.6	1.5	1.9	1.7
Ishak fibrosis score	2.2	2.1	2.5	2.3

Source: Table 11-18 of the Clinical Study Report

Baseline Knodell HIA, total or component mean scores, and Ishak fibrosis scores are shown in Table 11-18 of the Clinical Study Report. Total HAI scores ranged from 9-10 at baseline.

3.1.5 Applicant's Results and Statistical Reviewer's Findings

3.1.5.1 Primary Efficacy Analyses of Relative Risk of Laboratory-Confirmed, Symptomatic Influenza

The Primary Efficacy Endpoint was Therapeutic Response at Week 52, which was defined as:

- **Serum HBV DNA suppression < 5 log_{10} copies/mL at Week 52**

AND

- **HbeAg loss at Week 52 or ALT normalized at Week 52**

HBeAg loss at Week 52 was defined as loss of detectable serum HBeAg at Week 52 in a patient who was HBeAg+ at Baseline

ALT normalized at Week 52 was defined as ALT within normal limits at Week 52 for a patient with an elevated Alt level (> 1.0 × ULN) at either Baseline or Screening

Primary efficacy endpoint (Therapeutic Response at Week 52) by treatment and HBeAg status - ITT and EE populations

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	95.68% CI*	p-value†
ITT population				
HBeAg-positive	310/463 (67.0)	345/458 (75.3)	2.4, 14.2	0.0047
HBeAg-negative	173/224 (77.2)	167/222 (75.2)	-10.2, 6.1	0.6187
EE population				
HBeAg-positive	299/445 (67.1)	334/434 (77.0)	4.0, 15.9	0.0007
HBeAg-negative	180/223 (80.8)	174/228 (76.3)	-12.3, 3.3	0.2461

Source: Table 11-21 of the Clinical Study Report

*CI adjusted for multiple comparison to test treatment/antigen status interaction with an α level of 0.0432

†Treatment group differences controlled for randomization strata: difference between proportions for categorical variables

EE= Efficacy Evaluable Population

Non-inferiority Margin=-15%

Using the 3-step statistical test procedure described in Lu and Huque [Biometrical Journal 43 (2001) 7, 909-923] separate analyses were performed in the HBeAg-positive and HBeAg-negative populations.

Overall, based on the data submitted, the following results were observed in the pivotal phase III study (NV-02B-007) for the primary endpoint:

- In the HBeAg-positive subgroup of the ITT population 67% of the lamivudine subjects and 75% of the telbivudine subjects had a therapeutic response at Week 52 [95.68% confidence interval = (+2, +14), p=0.0047].

- In the HBeAg-negative subgroup of the ITT population, 77% of the lamivudine subjects and 75% of the telbivudine subjects had a therapeutic response at Week 52 [95.68% confidence interval = (-10, +6), p=0.6187].

Non-inferiority was demonstrated for telbivudine in both the ITT and EE populations. Compared to lamivudine, statistically significant treatment differences in favor of telbivudine were also observed in the HBeAg-positive subpopulation.

The applicant also claimed to have demonstrated that LdT was superior to lamivudine in the HBeAg-positive subgroup because they pre-specified that if non-inferiority was established they would test for superiority (i.e., superiority is established if the lower bound of the 95% confidence interval was > 0). However since superiority for the same endpoints was not demonstrated in the HBeAg-negative subpopulation, the DAVP will require replication of the superiority findings in the HBeAg-positive subgroup in another study before allowing Idenix to make this claim in the label.

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Proportion of patients with Therapeutic Response by study visit (all visits from weeks 12 to 52), by HBeAg status and by treatment – ITT population

	Lamivudine	Telbivudine
HBeAg-positive		
Week 12	206/463 (44.5%)	213/458 (46.5%)
Week 24	293/463 (63.3%)	308/458 (67.2%)
Week 32	307/463 (66.3%)	329/458 (71.8%)
Week 40	310/463 (67.0%)	351/458 (76.6%)
Week 48	309/463 (66.7%)	343/458 (74.9%)
Week 52	310/463 (67.0%)	345/458 (75.3%)
Week 60	209/354 (59.0%)	271/351 (77.2%)
Week 68	115/208 (55.3%)	163/206 (79.1%)
Week 76	95/165 (57.6%)	123/163 (75.5%)
HBeAg-negative		
Week 12	137/224 (61.2%)	140/222 (63.1%)
Week 24	165/224 (73.7%)	169/222 (76.1%)
Week 32	167/224 (74.6%)	174/222 (78.4%)
Week 40	165/224 (73.7%)	171/222 (77.0%)
Week 48	169/224 (75.4%)	172/222 (77.5%)
Week 52	173/224 (77.2%)	167/222 (75.2%)
Week 60	108/142 (76.1%)	103/142 (72.5%)
Week 68	65/98 (66.3%)	68/98 (69.4%)
Week 76	47/67 (70.1%)	51/68 (75.0%)

Source: Table 11-23 of the Clinical Study Report

The percentage of patients with a therapeutic response was higher in the telbivudine treatment group than in the control arm at each week in the HBeAg-positive subpopulation and at every week except Weeks 52 and 60 in the HBeAg-negative subpopulation.

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3.1.5.2 Robustness of Primary Efficacy Analyses

Summary of Applicant's Sensitivity Analysis Data

The applicant performed sensitivity analyses for missing data by excluding patients with missing values (Tables 14.2.1.30, 14.2.1.31, 14.2.1.32 and 14.2.1.33 of the Clinical Study Report). The applicant claims that these analyses confirmed the superiority of telbivudine treatment in the HBeAg-positive group and the non-inferiority of telbivudine treatment in the HBeAg-negative group.

The applicant also computed odds ratios for treatment effects in both the ITT and EE populations (Tables 14.2.2.3, 14.2.2.4, 14.2.2.5 and 14.2.2.6 of the Clinical Study Report). Using this approach, the applicant confirmed the superiority of telbivudine treatment in the HBeAg-positive group and the non-inferiority of telbivudine treatment in the HBeAg-negative group.

CMH Analysis of Primary efficacy endpoint (Therapeutic Response at Week 52) by treatment and HBeAg status - ITT population

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	p-value†
ITT population			
HBeAg-positive	310/463 (67.0)	345/458 (75.3)	0.0049
HBeAg-negative	173/224 (77.2)	167/222 (75.2)	0.6191

Source: Table 11-21 of the Clinical Study Report
† CMH p-value from SAS proc freq controlled for randomization strata

Similar results for the primary efficacy endpoint were obtained using proc freq in SAS by the statistical reviewer. The Breslow-Day tests of homogeneity of the odds ratio across HBeAg-Positive and HBeAg-Negative subpopulations was statistically significant at the pre-specified α=0.15 level (p=0.0503).

Primary efficacy endpoint (Therapeutic Response at Week 52) by treatment and HBeAg status – ITT using correct HBeAg classifications (instead of IVRS classifications)

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	95.68% CI*	p-value†
ITT population				
HBeAg-positive	302/455 (66.4)	336/445 (75.5)	3.3, 15.2	0.002
HBeAg-negative	181/232 (78.0)	176/235 (74.9)	-11.1, 4.8	0.424

Source: Statistical Reviewer's Analysis

*CI adjusted for multiple comparison to test treatment/antigen status interaction with an α level of 0.0432

†Treatment group differences controlled for randomization strata: difference between proportions for categorical variables

Non-inferiority Margin=-15%

The statistical reviewer repeated the primary analysis assigning patients to the correct HBeAg subpopulations and found nearly the same proportion of patients in each treatment group in the two subpopulations and no difference in the determination of non-inferiority or superiority for telbivudine in either subpopulation.

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3.1.5.3 Secondary Efficacy Analyses

Knodell HAI categories and scores

Categories	Scoring
Knodell system	
I: Periportal and/or bridging necrosis	0, 1, 3, 4, 5, 6, 10
II: Intralobular degeneration and focal necrosis	0, 1, 3, 4
III: Portal inflammation	0, 1, 3, 4
IV: Fibrosis	0, 1, 3, 4

Categories	Scoring
Necroinflammatory score (sum of I-III)	0-18 (sum of components I-III)
Total HAI score (sum of I-IV)	0-22 (sum of components I-IV)
Ishak system	
Fibrosis score	0, 1, 2, 3, 4, 5, 6

Source: Table 9-6 of the Clincial Study Report and SAP Section. 2.3.2 (Appendix 16.1.9)

A Histologic Response at Week 52 was defined as a 2-point or greater reduction in Knodell necroinflammatory score, with no worsening in Knodell fibrosis score.

Histologic Response by treatment group - mITT and mEE populations

Population	Lamivudine n/N (%)	Telbivudine n/N (%)	CI*	p-value†
mITT population				
HBeAg-positive	244/433 (56.3)	284/439 (64.7)	2.0, 14.7	0.0105
HBeAg-negative	144/218 (66.0)	141/212 (66.6)	-8.3, 9.5	0.8994
mEE population				
HBeAg-positive	237/386 (61.3)	274/384 (71.5)	3.6, 16.8	0.0024
HBeAg-negative	144/207 (69.7)	141/199 (70.8)	-7.7, 10.0	0.7984

Source: Table 11-24 of the Clinical Study Report
*95.68% CI for antigen status groups; 99.9067% CI for totals.
†Treatment group differences controlled for randomization strata: difference between proportions for categorical variables.
mITT = Modified ITT population with evaluable pre-treatment liver biopsies
mEE= Modified Efficacy Evaluable Population

Non-inferiority Margin=-15%

Compared to lamivudine patients, a significantly greater proportion of telbivudine patients in the HBeAg-positive subpopulation experienced a histologic response. The non-inferiority of telbivudine to lamivudine was demonstrated in the HBeAg-negative population.

As stated in the applicant's SAP, patients with missing or unevaluable Week 52 biopsy samples were also excluded from the analyses of histologic response in the mITT and mEE populations. The results were similar to those obtained above (Tables 14.2.1.30 – 14.2.1.33 of the Clinical Study Report).

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Histological Improvement at Week 52 (007 GLOBE Study)

	HBeAg-positive (n =797)		HBeAg-negative (n =417)	
	Telbivudine 600 mg (n=399)[1]	Lamivudine 100 mg (n=398)[1]	Telbivudine 600 mg (n=205)[1]	Lamivudine 100 mg (n=212)[1]
Histologic Response [2]				
Improvement	69%	60%	69%	68%
No Improvement	19%	26%	23%	25%
Missing Week 52 Biopsy	12%	15%	8%	7%

Source: Reviewer's Analyses

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥ 2

[2] Histologic Response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score

For labeling purposes, the statistical reviewer also summarized Histologic Response using patients with baseline Knodell Necroinflammatory Scores of at least 2 points in the mEE population. Results were similar to those obtained by the applicant using patients with baseline total HAI scores>3.

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Summary of change in Knodell score at Week 52 by treatment group - mITT and mEE populations

	HBeAg-positive		HBeAg-negative	
	Lamivudine	Telbivudine	Lamivudine	Telbivudine
mITT, N	433	439	218	212
Improvement, n (%)	244 (56)	284 (65)	144 (66)	141 (67)
No improvement, n (%)	125 (29)	100 (23)	56 (26)	53 (25)
Missing Week 52 Biopsy	64 (15)	55 (13)	18 (8)	18 (8)
mEE, N	386	384	207	199
Improvement, n (%)	237 (61)	274 (71)	144 (70)	141 (71)
No improvement, n (%)	93 (24)	64 (17)	49 (24)	41 (21)
Missing Week 52 Biopsy	56 (15)	46 (12)	14 (7)	17 (9)

Source: Same as Table 11-25 of the Clinical Study Report except this table also has the number and percentage of patients with Missing Week 52 Biopsies and has separated No Improvement into No Change and Worsening. Improvement=Histologic Response, No Improvement=No Histologic Response

Compared to lamivudine, approximately 10% more telbivudine patients in the HBeAg-positive subpopulation were rated as showing improvement in Knodell scores. The distribution of patients with improvement in Knodell scores at Week 52 was very similar in telbivudine and lamivudine treatment groups in the HBeAg-negative subpopulation.

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Summary of change in Knodell score at Week 52 by treatment group - mITT population

	HBeAg-positive		HBeAg-negative	
	Lamivudine	Telbivudine	Lamivudine	Telbivudine
mITT, N	433	439	218	212
Improvement, n (%)	244 (56)	284 (65)	144 (66)	141 (67)
No Change, n (%)	125 (29)	100 (23)	56 (26)	53 (25)
Worsening	64 (15)	55 (13)	18 (8)	18 (8)

Source: Statistical Reviewer's Analysis.
Improvement=Histologic Response

The statistical reviewer used SAS proc freq to compare row means scores for the three ordinal categories of change in Knodell score (CMH analysis stratified by baseline ALT strata). The p-value for the treatment difference in the HBeAg-positive subpopulation was close to being statistically significant in favor of telbivudine (compared to lamivudine) (p=0.06). There was no statistically significant treatment difference (p=0.55) in the HBeAg-negative subpopulation.

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The Knodell Histology Activity Index (HAI) is a method of categorizing and scoring liver disease severity from liver biopsies.

Biopsies were graded in four categories: periportal necrosis, intralobular necrosis, portal inflammation and fibrosis.

The Knodell HAI score was the sum of the four categories.

The maximum Knodell HAI score was 22 points.

The Knodell necroinflammatory score was the sum of the periportal necrosis, intralobular necrosis and portal inflammation scores (excluding fibrosis score).

Table 2-1 in the SAP presented the score range for the categories and composite scores.

For all score categories, a higher score indicates increased severity of disease.

Knodell HAI Categories and Scores

Categories	Scoring
Periportal +/- bridging necrosis	0, 1, 3, 4, 5, 6, 10
Intralobular degeneration and focal necrosis	0, 1, 3, 4
Portal inflammation	0, 1, 3, 4
Fibrosis	0, 1, 3, 4
Knodell necroinflammatory score	0 - 18
Knodell HAI score	0 - 22

Source: Table 2-1 of the SAP

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Total Knodell HAI scores, Knodell necroinflammatory scores, and component scores: changes at Week 52 – HBeAg-positive mITT and mEE populations

	Lamivudine			Telbivudine		
Knodell category	Baseline	Week 52	Change	Baseline	Week 52	Change
mITT population	n=433	n=369	n=369	n=439	n=384	n=384
Component I mean score	2.8	1.4	-1.43	2.8	1.2	-1.59
Component II mean score	1.9	0.9	-1.03	2.1	0.9	-1.21
Component III mean score	2.6	1.8	-0.79	2.6	1.8	-0.82
Component IV mean score	1.6	1.3	-0.40	1.5	1.2	-0.30
Necroinflammatory mean score	7.3	4.1	-3.24	7.4	3.8	-3.62
Total HAI score	9.0	5.4	-3.64	8.9	5.0	-3.92
mEE population	n=386	n=330	n=330	n=384	n=338	n=338
Component I mean score	3.0	1.5	-1.58	3.0	1.2	-1.80
Component II mean score	2.0	0.9	-1.12	2.2	0.9	-1.35
Component III mean score	2.8	1.9	-0.87	2.8	1.8	-0.99
Component IV mean score	1.7	1.3	-0.46	1.6	1.2	-0.36
Necroinflammatory mean score	7.8	4.3	-3.57	8.0	3.9	-4.13
HAI mean score	9.5	5.6	-4.02	9.5	5.1	-4.49

Source: Table 11-26 of the Clinical Study Report
Note: Necroinflammatory score is the sum of components I, II, and III; total HAI score is the sum of components I through IV. Component IV is the fibrosis component score.

Telbivudine total HAI, necroinflammatory, components I – III mean change from baseline scores appeared to be somewhat lower (better) than those for lamivudine. However the opposite was true for fibrosis (component IV).

Total Knodell HAI scores, Knodell necroinflammatory scores, and component scores: changes at Week 52 – HBeAg-negative mITT and mEE populations

Knodell category	Baseline	Week 52	Change	Baseline	Week 52	Change
mITT population	n=218	n=200	n=200	n=212	n=194	n=194
Component I mean score	2.9	1.4	-1.46	2.8	1.2	-1.62
Component II mean score	2.0	1.0	-1.02	1.9	0.9	-1.04
Component III mean score	2.7	1.9	-0.82	2.6	1.7	-0.89
Component IV mean score	1.9	1.5	-0.44	1.7	1.4	-0.30
Necroinflammatory mean score	7.6	4.3	-3.29	7.3	3.7	-3.55
Total HAI score	9.6	5.8	-3.73	9.0	5.1	-3.85
mEE population	n=207	n=193	n=193	n=199	n=182	n=182
Component I mean score	3.0	1.4	-1.52	3.0	1.2	-1.79
Component II mean score	2.1	1.0	-1.10	2.0	0.9	-1.08
Component III mean score	2.8	1.9	-0.87	2.7	1.7	-0.97
Component IV mean score	2.0	1.5	-0.41	1.8	1.5	-0.37
Necroinflammatory mean score	7.9	4.3	-3.48	7.7	3.8	-3.84
HAI mean score	9.8	5.8	-3.89	9.5	5.3	-4.21

Source: Table 11-27 of the Clinical Study Report
Note: Necroinflammatory score is the sum of components I, II, and III; total HAI score is the sum of components I through IV. Component IV is the fibrosis component score.

The statistical reviewer used a mixed model adjusted for baseline ALT strata and baseline Knodell Fibrosis Score to compare changes in Knodell Fibrosis (Component IV) scores in the two treatment groups. There was no statistically significant treatment difference (p=0.71) for the HBeAg-positive subpopulation and no statistically significant treatment difference (p=0.49) for the HBeAg-negative subpopulation.

The statistical reviewer used a mixed model adjusted for baseline ALT strata and baseline Necroinflammatory Score to compare changes in Necroinflammatory mean scores in the two treatment groups and found the difference between telbivudine and lamivudine was close to being statistically significant (p=0.054) in favor of telbivudine in the HBeAg-Positive subpopulation and was statistically significant (p=0.046) in favor of telbivudine in the HBeAg-Negative subpopulation.

The Ishak Fibrosis Score

- **a 7-point (0-6) continuous integer scale**
- **ranging from 0 (no Fibrosis) to 6 (Cirrhosis; probable or definite).**

Ishak Fibrosis Score

Categories	Scoring
Ishak Fibrosis Score	0, 1, 2, 3, 4, 5, 6

Source: Table 2-2 of the SAP

Change in Ishak Fibrosis Scores was categorized as:

- **Improvement: ≥1-point Decrease from Baseline**
- **Worsening: ≥1-point Increase from Baseline**
- **No Change: Post-Baseline score = Baseline Score**

Table 11-28 Ishak fibrosis score changes by treatment group - mITT and mEE populations

Change	Lamivudine	Telbivudine	95% CI	p-value*
mITT HBeAg-positive	N=433	N=439		
Improved, n (%)	189 (43.6)	166 (37.8)	-12.3, 0.6	0.0774
No change, n (%)	143 (33)	175 (40)		
Worsened, n (%)	37 (9)	43 (10)		
Missing Week 52 biopsy, n (%)	64 (15)	55 (13)		
mITT HBeAg-negative	N-218	N=212		
Improved, n (%)	99 (45.4)	100 (47.1)	-7.7, 11.1	0.7209
No change, n (%)	90 (41)	69 (33)		
Worsened, n (%), n(%)	11 (5)	25 (12)		
Missing Week 52 biopsy, n (%)	18 (8)	18 (8)		
mEE HBeAg-positive	N=386	N=384		
Improved, n (%)	181 (46.8)	160 (41.8)	-12.0, 2.0	0.1601
No change, n (%)	122 (32)	148 (39)		
Worsened, n (%)	27 (7)	30 (8)		
Missing Week 52 biopsy, n (%)	56 (15)	46 (12)		
mEE HBeAg-negative	N=207	N=199		
Improved, n (%)	93 (44.9)	97 (48.8)	-5.8, 13.6	0.4290
No change, n (%)	89 (43)	67 (34)		
Worsened, n (%)	11 (5)	18 (9)		
Missing Week 52 biopsy, n (%)	14 (7)	17 (9)		

*Treatment group differences controlled for randomization strata: difference between proportions

Source: Table 11-28 of the Clinical Study Report
Non-inferiority Margin=-8%

Ishak Fibrosis scores for telbivudine did not meet the pre-specified non-inferioritiy criterion (lower limit of the 95% confidence interval > -8%) for HBeAg-positive patients but did so for HBeAg-negative patients. In addition, the p-value for the difference between telbivudine and lamivudine was 0.0774, so the difference in favor of lamivudine over telbivudine in HBeAg-positve patients was almost statistically significant. This was a surprising finding because telbivudine appeared non-inferior or superior to lamivudine in the HBeAg-positive subpopulation for many of the other endpoints.

The statistical reviewer also analyzed the 3 ordinal categories of Ishak Fibrosis score in the ITT population using the row-mean score statistic from proc freq in SAS excluding patients with missing values from the analysis. The treatment difference was almost statistically significant for the HBeAg-Positive subpopulation (p=0.051; CMH analysis stratified by baseline ALT strata) while the treatment difference was not statistically significant in the HBeAg-negative subpopulation (p=0.41).

Change in Ishak Fibrosis Score at Week 52 (007 GLOBE Study)

	HBeAg-positive (n =797)		HBeAg-negative (n =417)	
	Telbivudine 600 mg (n=399)[1]	Lamivudine 100 mg (n=398)[1]	Telbivudine 600 mg (n=205)[1]	Lamivudine 100 mg (n=212)[1]
Ishak Fibrosis Score[2]				
Improvement	41%	46%	48%	44%
No Change	39%	32%	34%	43%
Worsening	9%	7%	10%	5%
Missing Week 52 Biopsy	12%	15%	8%	7%

Source: Reviewer's Analyses

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥ 2

[2]For Ishak Fibrosis Score, improvement defined as a ≥ 1-point reduction in Ishak fibrosis score from Baseline to Week 52

For labeling purposes, the statistical reviewer also summarized Ishak Fibrosis Score using patients with baseline Knodell Necroinflammatory Scores of at least 2 points in the mEE population. Results were similar to those obtained by the applicant using patients with baseline total HAI scores>3.

Table 11-29 Summary of changes in Ishak fibrosis score based on Baseline Ishak fibrosis score - mITT populations

	HBeAg-positive		HBeAg-negative	
	Lamivudine	Telbivudine	Lamivudine	Telbivudine
mITT Baseline score >3				
N	41	31	26	27
Mean (SE)	-1.2 (0.23)	-1.4 (0.23)	-1.1 (0.26)	-1.2 (0.26)
Median	-1.0	-1.0	-1.0	-1.0
25%, 75%	-2.0, 0.0	-2.0, -1.0	-2.0, 0.0	-2.0, 0.0
Min, Max	-5.0, 2.0	-4.0, 2.0	-5.0, 0.0	-4.0, 2.0
mITT Baseline score ≤3				
N	328	353	174	167
Mean (SE)	-0.5 (0.05)	-0.3 (0.04)	-0.5 (0.06)	-0.4 (0.08)
Median	0.0	0.0	0.0	0.0
25%, 75%	-1.0, 0.0	-1.0, 0.0	-1.0, 0.0	-1.0, 0.0
Min, Max	-3.0, 3.0	-3.0, 3.0	-2.0, 2.0	-2.0, 3.0

Source: Table 11-29 of the Clinical Study Report

The applicant also summarized changes in Ishak fibrosis score to assess treatment effects in patients with bridging fibrosis or cirrhosis (baseline score >3) versus patients with early-stage disease (baseline score ≤3). Most patients had early-stage disease and in these patients there was less improvement for telbivudine patients (in the mean change from baseline scores) than for lamivudine patients, particularly in the HBeAg-positive subpopulation (-0.5 for lamivudine vs. -0.3 for telbivudine).

The statistical reviewer used a mixed model adjusted for baseline ALT strata to compare changes in Ishak Fibrosis Scores in the two treatment groups. Among patients with low baseline Ishak Fibrosis scores (0-3), there was a statistically significant difference (p=0.026) between telbivudine and lamivudine in the HBeAg-positive subpopulation and no statistically significant treatment difference (p=0.38) for the HBeAg-negative subpopulation.

There were no statistically significant treatment group differences in either HBeAg subpopulation among patients with high baseline Ishak Fibrosis scores (≥3) (p=0.61 in the HBeAg-Positive subpopulation and p=0.74 in the HBeAg-Negative subpopulation).

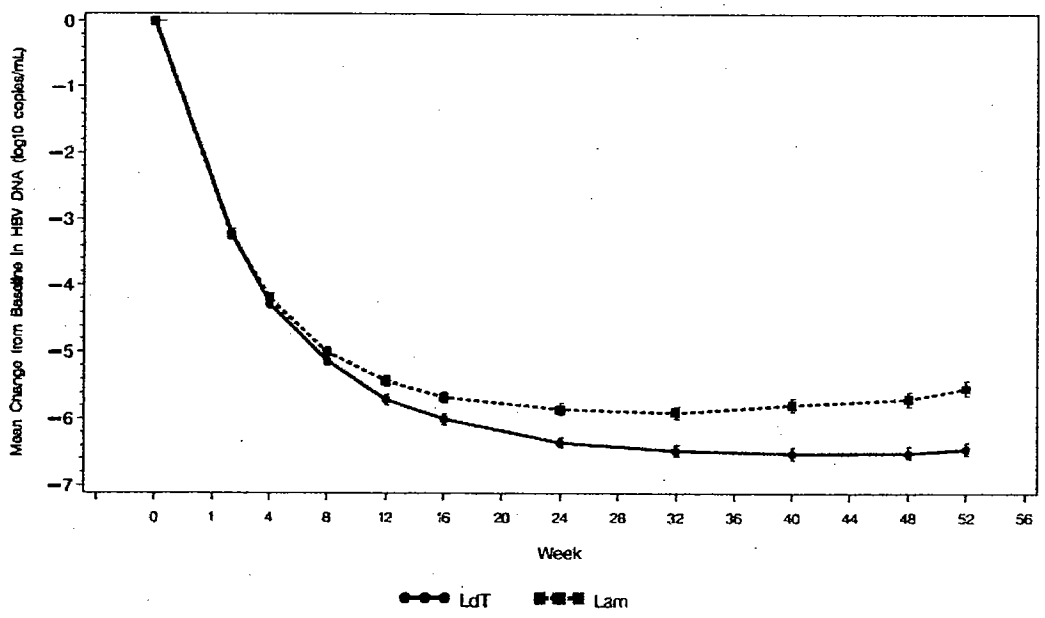
HBV DNA reduction (log_{10} copies/mL) from Baseline at Weeks 24 and 52 - ITT population
AMENDED

	HBeAg-positive			HBeAg-negative		
Time point	Lamivudine N=463	Telbivudine N=458	p-value	Lamivudine N=224	Telbivudine N=222	p-value
Week 24	n=453	n=450		n=221	n=222	
mean (SE)	-5.9 (0.09)	-6.4 (0.08)	<0.0001	-4.8 (0.11)	-5.2 (0.11)	0.0023
median	-6.0	-6.5		-4.7	-4.9	
Week 52	n=444	n=443		n=219	n=219	
mean (SE)	-5.5 (0.12)	-6.4 (0.09)	<0.0001	-4.4 (0.14)	-5.2 (0.13)	<0.0001
median	-5.9	-6.7		-4.5	-5.0	

Source: Table 11-30 of the Clinical Study Report
Note: observations after treatment discontinuation due to efficacy and initiation of nonstudy anti-HBV drugs excluded.

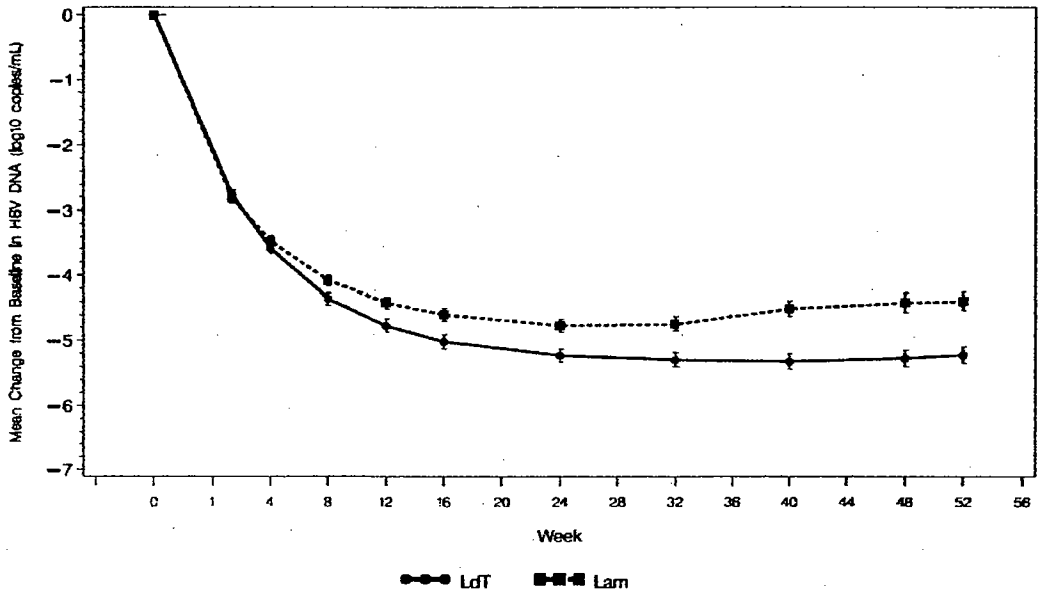
Mean HBV DNA reductions from baseline were significantly larger for telbivudine patients in both HBeAg subpopulations at Weeks 24 and 52.

Figure 11-1 Mean change (+/-SE) from Baseline to Week 52 in HBV DNA levels by treatment group - HBeAg-positive ITT population



LdT = telbivudine, LAM = lamivudine
Note: LOCF for missing data due to early study withdrawal and intermittent missing data.
Source: Figure 11-1 of the Clinical Study Report

Figure 11-2 Mean change (+/-SE) from Baseline to Week 52 in HBV DNA levels by treatment group - HBeAg-negative ITT population



LdT = telbivudine, LAM = lamivudine

Note: LOCF for missing data due to early study withdrawal and intermittent missing data.

Source: Figure 11-2 of the Clinical Study Report

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Proportion of patients who achieved specific HBV DNA levels at Week 24 and Week 52, by HBeAg status – ITT population

	HBeAg-positive		HBeAg-negative	
Time point	Lamivudine (N=463)	Telbivudine (N=458)	Lamivudine (N=224)	Telbivudine (N=222)
Week 24	n=453	n=450	n=221	n=222
<3 log10	209 (46.1)	260 (57.8)	177 (80.1)	196 (88.3)
<4 log10	288 (63.6)	343 (76.2)	201 (91.0)	212 (95.5)
<5 log10	366 (80.8)	414 (92.0)	211 (95.5)	219 (98.6)
≥5 log10	87 (19.2)	36 (8.0)	10 (4.5)	3 (1.4%)
Week 52	n=444	n=443	n=219	n=219
<3 log10	219 (49.3)	308 (69.5)	174 (79.5)	198 (90.4)
<4 log10	279 (62.8)	351 (79.2)	186 (84.9)	206 (94.1)
<5 log10	337 (75.9)	403 (91.0)	196 (89.5)	211 (96.3)
≥5 log10	107 (24.1)	40 (9.0)	23 (10.5)	8 (3.7)

Source: Table 11-31 of the Clinical Study Report
Note: observations after treatment discontinuation due to efficacy and initiation of nonstudy anti-HBV drugs excluded.

Compared to lamivudine, the proportion of patients with HBV DNA levels less than 3, 4, and 5 $\log_{10}$ copies/mL was consistently higher in telbivudine patients in both HBeAg subpopulations at Weeks 24 and 52. Many of these differences were statistically significant; for example, at Week 52 for the minimum response threshold of 5 $\log_{10}$ copies/mL, $p<0.001$ in the HBeAg-positive subpopulation and $p=0.005$ in the HBeAg-negative subpopulation.

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Undetectable HBV DNA (PCR Negative) was defined as:

- **HBV DNA < 300 copies/mL, the lower limit of quantitation (LLOQ) of the COBAS Amplicor HBV Monitor™ assay**

Proportion of patients with PCR-nondetectable HBV DNA by study visit, by HBeAg status - ITT population

	HBeAg-positive			HBeAg-negative		
Time point	Lamivudine N=463	Telbivudine N=458	p-value*	Lamivudine N=224	Telbivudine N=222	p-value*
Week 24, n (%)	146 (31.6)	203 (44.3)	0.0001	157 (70.1)	178 (80.2)	0.0129
Week 52, n (%)	187 (40.4)	275 (60.0)	<0.0001	160 (71.4)	196 (88.3)	<0.0001

Source: Table 11-32 of the Clinical Study Report
*Treatment group differences controlled for randomization strata: difference between proportions for categorical variables.

Compared to lamivudine, the proportion of patients with PCR-nondetectable HBV DNA at Weeks 24 and 52 was significantly higher in telbivudine patients.

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Maintained Undetectable HBV DNA (Maintained PCR Negative) was defined as:

- **HBV DNA < 300 copies/mL for at least two consecutive visits**
- **and at the patient's last treatment visit**
- **with no two intervening consecutive visits where a patient had HBV DNA ≥ 300 copies/mL**

A visit could be scheduled or unscheduled.

Missing values were not considered.

Time to Maintained Undetectable HBV DNA was defined as:

- **Time from Baseline to the first of the two consecutive visits**
- **For patients who met the Maintained HBV Non-Detectable Endpoint**

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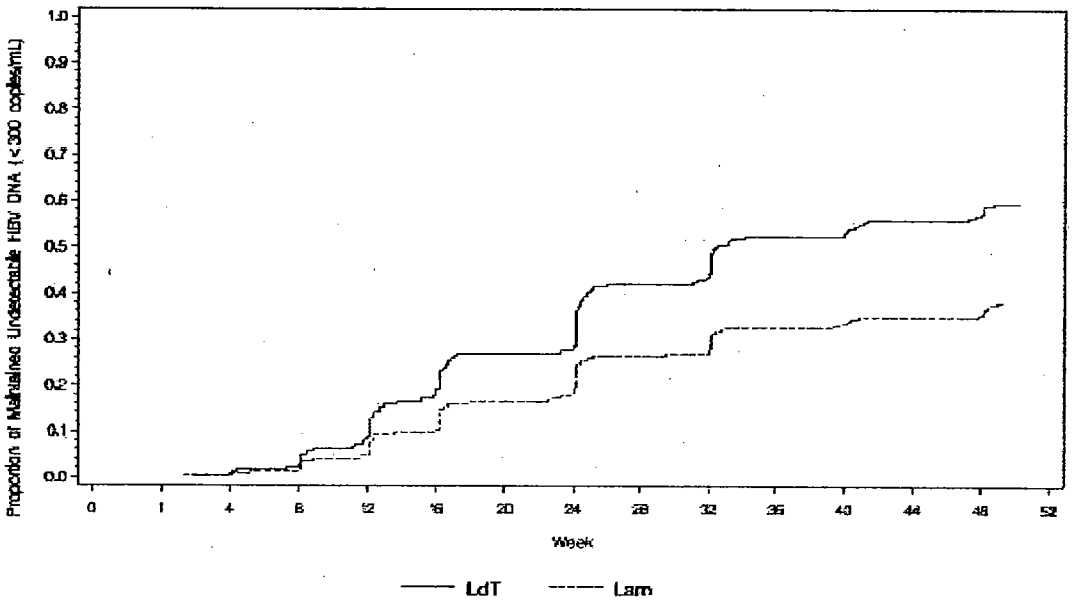
Figure 11-3 Time to maintained undetectable HBV DNA - HBeAg-positive ITT population



LdT = telbivudine, LAM = lamivudine

Note: Analysis censored at the earlier date of Week 52, treatment discontinuation date (including due to efficacy), or onset of on-treatment nonstudy HBV medication. Event time is Baseline to the starting time of the event.

Source: Figure 11-3 of the Clinical Study Report

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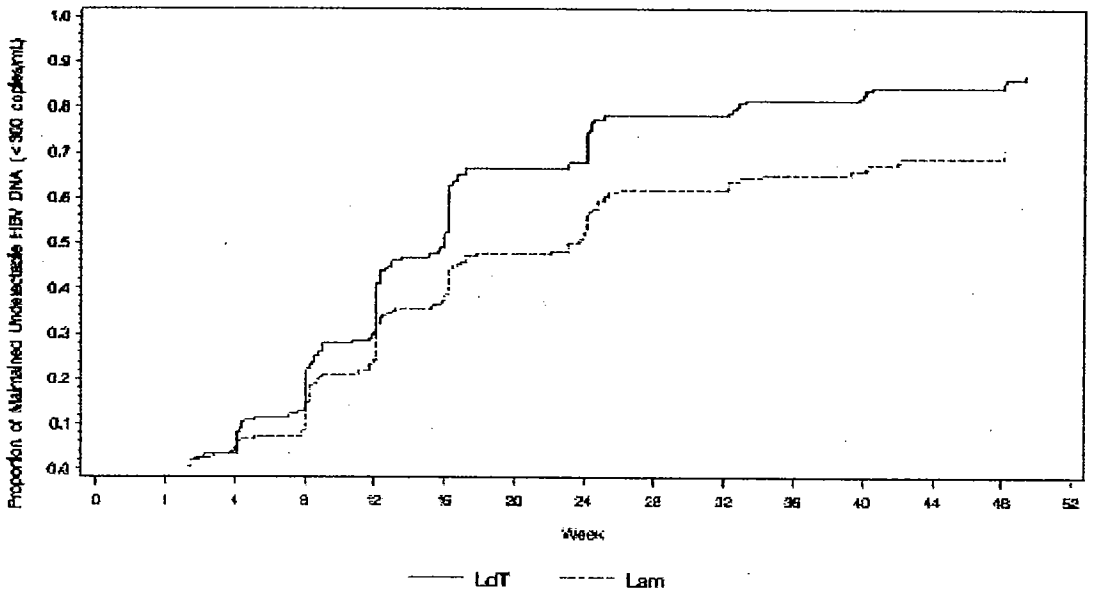
Figure 11-4 Time to maintained undetectable HBV DNA - HBeAg-negative ITT population



LdT = telbivudine, LAM = lamivudine

Note: Analysis censored at the earlier date of Week 52, treatment discontinuation date (including due to efficacy), or onset of on-treatment nonstudy HBV medication. Event time is Baseline to the starting time of the event.

Source: Figure 11-4 of the Clinical Study Report

There was also an earlier time to maintained undetectable HBV DNA in both HBeAg subpopulations for telbivudine compared to lamivudine as shown in Kaplan-Meier Plots in Figures 11-3 and 11-4 ($p<0.001$ in both subpopulations: For details, see tables 14.2.11.5 and 14.2.11.6 in the Clinical Study Report).

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Table 14.2.11.5
Time to Maintained HBV DNA Non-Detectable Response (<300 copies/mL) at Week 52
Intent-To-Treat HBeAg Positive Population

	Lam (N=463)	LdT (N=458)	Total (N=921)
Number of Events (%)	176 (38.0)	268 (58.5)	444 (48.2)
Number censored (%)	287 (62.0)	190 (41.5)	477 (51.8)
Mean (SE)	39 (0.7)	34 (0.8)	37 (0.5)
25th percentile (95% CI)	24 (24, 32)	17 (16, 24)	24 (23, 24)
Median (95% CI)	NE (NE, NE)	32 (32, 41)	NE (48, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Minimum	2	2	2
Maximum	49	50	50
P-value (1)		<0.001	

Source: Table 14.2.11.5 of the Clinical Study Report

Table 14.2.11.6
Time to Maintained HBV DNA Non-Detectable Response (<300 copies/mL) at Week 52
Intent-To-Treat HBeAg Negative Population

	Lam (N=224)	LdT (N=222)	Total (N=446)
Number of Events (%)	156 (69.6)	192 (86.5)	348 (78.0)
Number censored (%)	68 (30.4)	30 (13.5)	98 (22.0)
Mean (SE)	26 (1.1)	20 (1.0)	23 (0.8)
25th percentile (95% CI)	12 (9, 12)	9 (8, 12)	11 (8, 12)
Median (95% CI)	24 (16, 24)	16 (12, 16)	16 (16, 17)
75th percentile (95% CI)	NE (48, NE)	24 (24, 33)	40 (32, NE)
Minimum	2	2	2
Maximum	48	49	49
P-value (1)		<0.001	

Source: Table 14.2.11.6 of the Clinical Study Report

The percentage of patients with maintained HBV DNA Non-Detectable Response was only slightly lower than the percentage of all patients with PCR-nondetectable HBV DNA at Week 52 in Table 11-32.

HBeAg loss (HBeAg-positive subpopulation only) was defined as:

- **loss of detectable serum HBeAg**

HBeAg seroconversion (HBeAg-positive subpopulation only) was defined as:

- **HBeAg loss with detectable HBeAb**

HBeAg loss and seroconversion at weeks 24 and 52 - ITT population AMENDED

	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value*
HBeAg loss				
Week 24	65/442 (14.7)	69/432 (16.0)	-3.5, 6.0	0.5986
Week 52	103/442 (23.3)	111/432 (25.7)	-3.2, 8.1	0.4038
HBeAg seroconversion				
Week 24	59/442 (13.3)	65/432 (15.1)	-2.9, 6.3	0.4677
Week 52	95/442 (21.5)	97/432 (22.2)	-4.5, 6.4	0.7263

Source: Table 11-33 of the Clinical Study Report
*Treatment group differences controlled for randomization strata: difference between proportions
Non-inferiority Margin=-10% for HBeAg loss at Week 52
Non-inferiority Margin=-5.5% for HBeAg seroconversion at Week 52

Non-inferiority of telbivudine to lamivudine was demonstrated for HBeAg loss and HBeAg seroconversion at Week 52 (because the lower bound of the 95% CI was to the right of the pre-specified Non-inferiority margins of -10% and -5.5% respectively).

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HBeAg loss and seroconversion at weeks 24 and 52 using denominators from the primary analysis – ITT population

	Lamivudine n/N (%)	Telbivudine n/N (%)
HBeAg loss		
Week 24	65/463 (14.0)	69/458 (15.1)
Week 52	103/463 (22.2)	111/458 (24.2)
HBeAg seroconversion		
Week 24	59/463 (12.7)	65/458 (14.2)
Week 52	95/463 (20.5)	97/458 (21.2)

Source: Statistical Reviewer's Analysis

Similar results for HBeAg loss and HBeAg seroconversion were obtained by the statistical reviewer using the denominators from the primary analysis.

Virologic Response (HBeAg-positive subpopulation only) was defined as:

- **HBeAg loss and HBV DNA < 5 $\log_{10}$ copies/mL**

Proportion of patients with Virologic Response at Weeks 24 and 52 ITT Population

	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value*
ITT population				
Week 24	65/442 (14.7)	69/432 (16.0)	-3.5, 6.0	0.5986
Week 52	101/442 (22.8)	111/432 (25.7)	-2.8, 8.5	0.3197
EE population				
Week 24	68/433 (15.7)	68/420 (16.3)	-4.3, 5.5	0.8112
Week 52	102/433 (23.5)	114/420 (27.2)	-2.0, 9.5	0.2015

Source: Table 11-34 of the Clinical Study Report
Virologic Response is defined HBeAg loss and < 5 $\log_{10}$ HBV DNA. Thus, the Virologic Response is an endpoint defined only for the HBeAg-positive subpopulation.
*Treatment group differences controlled for randomization strata: ANOVA
Non-inferiority Margin=-10%

In the ITT population, the results for Virologic Response in Table 11-34 of the Clinical Study Report were the same as the results for HBeAg loss in Table 11-33 at Week 24 and almost the same at Week 52.

ALT normalization was defined as:

- **ALT within normal limits on two successive visits**
- **for a patient with elevated ALT (>1.0 × ULN) at Baseline**

A visit could be scheduled or unscheduled.

Missing values were not considered.

Proportion of patients with ALT normalization by study visit by antigen status - ITT population AMENDED

	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value*
HBeAg-positive				
Week 24	299/446 (67.0)	289/440 (65.6)	-7.6, 4.6	0.6273
Week 52	334/446 (74.9)	340/440 (77.2)**	-3.3, 7.9	0.4172
Week 76	108/160 (67.5)	126/161 (78.3)	(1.1, 20.4)	0.0290
HBeAg-negative				
Week 24	147/207 (71.0)	150/203 (73.9)	-5.8, 11.5	0.5208
Week 52	164/207 (79.3)**	151/203 (74.4)	-13.0, 3.2	0.2385
Week 76	39/61 (63.8)	50/66 (75.8)	(-3.8, 27.8)	0.1364

Source: Table 11-36 of the Clinical Study Report
*Treatment group differences controlled for randomization strata. Patients with ALT <1 x ULN at Baseline excluded from analysis.
**These values were computed from weighted percentages and differ from values in Table 11-50.
Non-inferiority Margin=-15%

Telbivudine was non-inferior to lamivudine for the proportion of patients with ALT normalization in both HBeAg subpopulations.

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Maintained ALT Normalization was defined as:

- **ALT Normalization for at least two consecutive visits**
- **and at the patient's last treatment visit**
- **with no intervening consecutive visits where a patient did not have ALT Normalization**

A visit could have been scheduled or unscheduled.
Missing values were not considered.

Time to Maintained Undetectable ALT Normalization was defined as:

- **Time from Baseline to the first of the two consecutive visits**

For patients who met the Maintained ALT Normalization Endpoint

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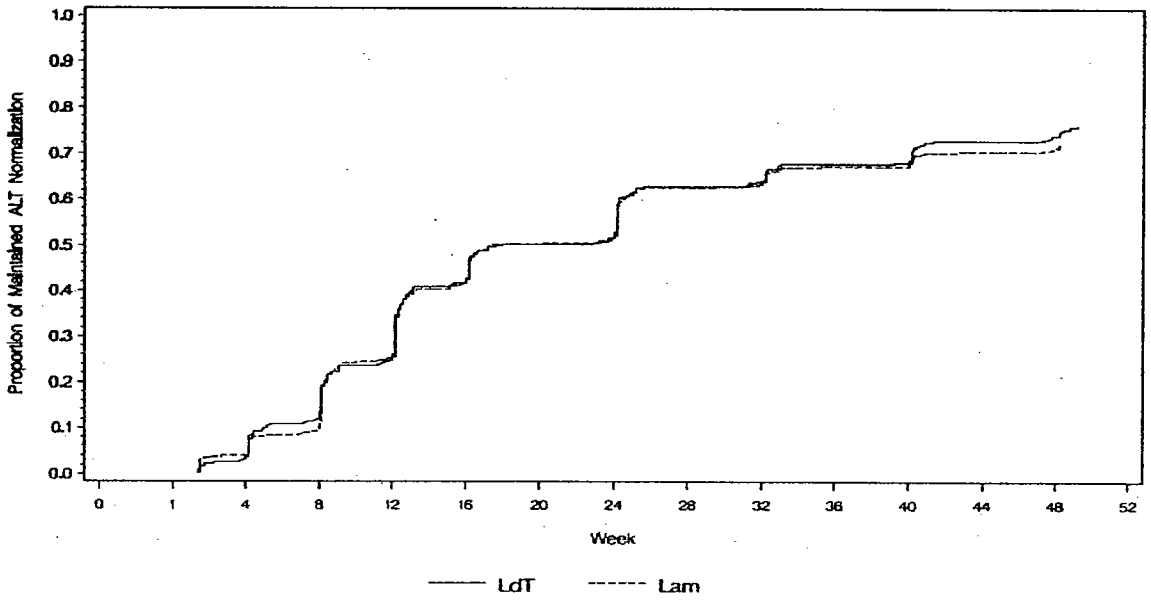
Figure 11-5 Time to maintained ALT normalization - HBeAg-positive ITT population



LdT = telbivudine; LAM = lamivudine
Note: Analysis censored at the earlier date of Week 52, treatment discontinuation for efficacy, or onset of nonstudy HBV medication.
Source: Figure 11-5 of the Clinical Study Report

Telbivudine also appeared comparable to lamivudine with respect to the time to maintained ALT normalization in both HBeAg subpopulations and there were no statistically significant differences between the two treatment groups (p=0.458 for HBeAg-positive patients and p=0.500 for HBeAg-negative patients; see Tables 14.2.15.8 and 14.2.15.9 of the Clinical Study Report).

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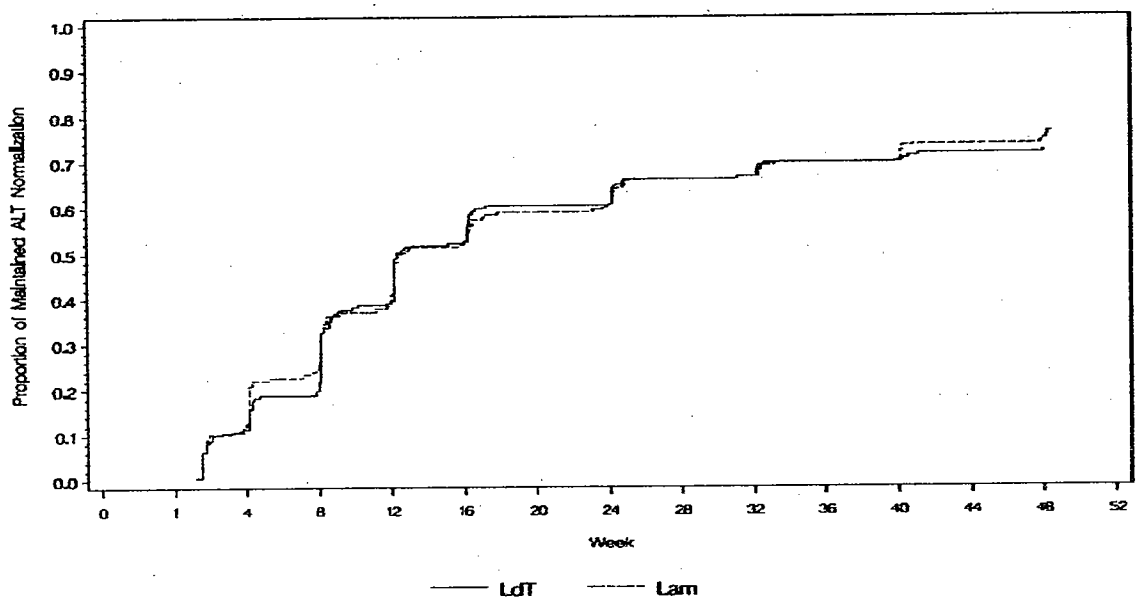
Figure 11-6 Time to maintained ALT normalization - HBeAg-negative ITT population



LdT = telbivudine; LAM = lamivudine
Note: Analysis censored at the earlier date of Week 52, treatment discontinuation for efficacy, or onset of nonstudy HBV medication.

Source: Figure 11-6 of the Clinical Study Report

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Treatment discontinuation for efficacy at Week 52 (ITT population)

	HBeAg-positive		HBeAg-negative	
	Lamivudine (N=463) n (%)	Telbivudine (N=458) n (%)	Lamivudine (N=224) n (%)	Telbivudine (N=222) n (%)
Qualified for treatment discontinuation*	38 (8.2)	43 (9.4)	3 (1.3)	2 (0.9)
Discontinuations for efficacy	4 (0.9)	9 (2.0)	1 (0.4)	0

Source: Table 11-37 of the Clinical Study Report
*Based on investigator assessment

In HBeAg-positive patients, 8.2% of the lamivudine patients qualified for treatment discontinuation according to protocol criteria at Week 52 compared to 9.4% of the telbivudine patients. However only 0.9% of the lamivudine patients and 2.0% of the telbivudine patients discontinued treatment due to efficacy at Week 52.

In the HBeAg-negative subpopulation only 3 of the 224 lamivudine patients and 2 of the 222 telbivudine patients qualified for treatment discontinuation and only 1 lamivudine patient and none of the telbivudine patients discontinued for lack of efficacy . The applicant noted that the protocol stated that treatment discontinuation due to efficacy in the HBeAg-negative subpopulation required at least 52 weeks of study treatment and HBsAg loss documented on two successive study visits.

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Virologic Breakthrough was defined based on the following criteria:

For patients who had Baseline serum HBV DNA ≥ 6 log_{10} copies/mL, and who:

1. ***While on treatment, achieved HBV DNA < 5 log_{10} copies/mL on two consecutive visits***

   - **A patient had HBV DNA ≥ 5 log_{10} copies/mL on two consecutive visits with no more than one more subsequent HBV DNA values <5 log_{10} copies/mL**
   - **Patient's HBV DNA value at the last treatment visit must also have been ≥ 5 log_{10} copies/mL**
   - **If a patient had a single qualifying HBV DNA value (≥ 5 log_{10} copies/mL) at the last treatment visit, this result also qualified as a Virologic Breakthrough.**

2. ***Did not achieve at least two consecutive HBV DNA values <5 log_{10} copies/mL, but who achieved a decrease in serum HBV DNA of at least 2 log_{10} copies/mL from Baseline on two consecutive visits***

   - **A patient did not have two consecutive HBV DNA <5 log_{10} copies/mL, but had a return of serum HBV DNA to within 1 log_{10} copies/mL of Baseline on two consecutive visits with no more than one subsequent value greater than 1 log_{10} copies/mL below Baseline through the last treatment visit**
   - **If a patient's serum HBV DNA returned to within 1 log_{10} copies/mL of Baseline at the last treatment visit, this result also qualified as a Virologic Breakthrough.**

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For the *Week 48 assessment*,

- **The analysis endpoint was the patient meeting the Virologic Breakthrough criteria at or prior to Week 48**
- **Week 52 was considered to be the last treatment visit in determining if a patient met the Virologic Breakthrough endpoint by Week 48.**
- **If a patient discontinued from the study or treatment prior to Week 52, the patient's last treatment date was used.**

HBV Resistance was defined as documented presence of resistance-associated mutations in HBV DNA amplified (by PCR methods) from the sera of patients with Virologic Breakthrough; the resistance-associated mutations were required to be "treatment emergent", i.e., the mutations were not present in the patients' pre-treatment (baseline) sera.

Virologic Breakthrough and Treatment-Emergent HBV Resistance at Week 48, by HBeAg status - ITT population

	HBeAg-positive			HBeAg-negative		
	Lamivudine N=442	Telbivudine N=438	p-value*	Lamivudine N=187	Telbivudine N=192	p-value*
Endpoint	n (%)	n (%)		n (%)	n (%)	
Virologic Breakthrough	46 (10.4)	15 (3.4)	<0.0001	16 (8.5)	4 (2.1)	0.0052
HBV Resistance	36 (8.2)	13 (3.0)	0.0007	16 (8.5)	4 (2.1)	0.0052

Source: Table 11-38 of the Clinical Study Report
*Treatment group differences controlled for randomization strata: ANOVA.
Non-inferiority Margin was not pre-specified. Only superiority testing was pre-specified.

All of the HBeAg-negative patients with virologic breakthrough were confirmed to have HBV resistance compared to only about 80% of the HBeAg-positive subpopulation.

In both HBeAg subpopulations, the percentage of telbivudine patients with virologic breakthough and HBV Resistance was significantly lower than the corresponding percentage of lamivudine patients.

However because Virologic Breakthrough was pre-specified to be tested after ALT Normalization, and telbivudine was not shown to be superior to lamivudine with respect to ALT

normalization, it is not valid to claim that telbivudine is superior to lamivudine in terms of Virologic Breakthrough.

The non-inferiority of telbivudine to lamivudine can be claimed for Virologic Breakthrough even though a non-inferiority margin was not pre-specified because the treatment difference was highly significant, implying that the confidence interval would be significantly greater than zero.

HBV Resistance did not appear on the hierarchical fixed hypothesis testing list so a claim of superiority for this endpoint is also unacceptable.

Treatment-emergent virologic rebound was defined in the microbiologist's review as virologic breakthrough with ≥ 1 $\log_{10}$ increase of HBV DNA from nadir while on therapy, which differs from the protocol definition of virologic breakthrough the Applicant utilized for their virologic breakthrough analyses. In addition, the microbiologist used the As Treated population (similar to the EE population) instead of the ITT population for her analyses. Using the microbiology reviewer's definition, the percentage of patients with virologic rebound (in Table 11 of the microbiology review) was approximately 3 times higher than the percentage of patients with virologic breakthrough in Table 11-38 of the Clinical Study Report in both lamivudine and telbivudine groups in the HBeAg-positive subgroup and approximately twice as high in the HBeAg-negative subgroup. For further details, see the microbiology review.

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A patient was considered to have a Primary Treatment Failure if

- **their HBV DNA values never fell to <5 log_{10} for at least two consecutive visits after the start of study treatment**
- **they completed at least 24 weeks of treatment**

A visit could have been scheduled or unscheduled.

Missing values were not considered.

Secondary Treatment Failures were defined by the following criteria (for more details, see pages 18-19 in Section 2.3.2 of the SAP):

- **Lack of Efficacy due to severe ALT elevations** (≥10 × ULN) **or persistently moderate ALT elevations** (≥ 2 × ULN) **with HBV Viremia** (serum HBV DNA ≥ 16 log_{10} copies/mL or serum HBV DNA pattern meets either of the Virologic Breakthrough Definitions)
- **Discontinued due to Clinically Significant Hepatic Disease Progression**
- **Study Discontinuation due to Lack of Efficacy**
- **Study Discontinuation Due to Patient, Investigator, or Sponsor Request with ALT Elevation** (≥2 × ULN) **and HBV Viremia** (serum HBV DNA ≥ 16 log_{10} copies/mL OR serum HBV DNA pattern meets either of the Virologic Breakthrough definitions)

Proportion of patients with primary or secondary treatment failure at Week 52 - ITT population

	HBeAg-positive			HBeAg-negative		
	Lamivudine	Telbivudine		Lamivudine	Telbivudine	
Failure type	n/N (%)	n/N (%)	p-value*	n/N (%)	n/N (%)	p-value*
Primary	61/454 (13.4)	21/450 (4.7)	<0.0001	6/222 (2.7)	1/222 (0.5)	0.0555
Secondary	13/463 (2.8)	3/458 (0.7)	0.0118	2/224 (0.9)	0/222 (0)	0.1554
Total	67/463 (14.4)	22/458 (4.8)	<0.0001	8/224 (3.6)	1/222 (0.5)	0.0180

Source: Table 11-39 of the Clinical Study Report
*Treatment group differences controlled for randomization strata: ANOVA
Non-inferiority Margin was not pre-specified. Only superiority testing was pre-specified.

Primary, secondary and total failure rates were significantly lower for telbivudine than lamivudine in the HBeAg-positive subpopulation. Telbivudine was also favored in the HBeAg-negative subpopulation although treatment differences were only statistically significant for total failures.

However because Primary Treatment Failure was pre-specified to be tested after ALT Normalization, and telbivudine was not shown to be superior to lamivudine with respect to ALT normalization, it is not valid to claim that telbivudine is superior to lamivudine.

The non-inferiority of telbivudine to lamivudine cannot be claimed for primary treatment failures in the HBeAg-positive subpopulation because non-inferiority for Change in Ishak Fibrosis Score was not achieved previously in the hierarchical testing procedure. Non-inferiority for telbivudine to lamivudine can also not be claimed for primary treatment failures in the HBeAg-negative subpopulation because non-inferiority margins were not pre-specified and the treatment difference was not statistically significant.

Telbivudine superiority and non-inferiority to lamivudine cannot be claimed for secondary treatment failures and total failures since these endpoints were not included in the hierarchical fixed hypothesis testing list.

Of note, virologic failure was defined in this review as failure to achieve HBV DNA suppression at Week 52. The FDA microbiologist's definition of HBV DNA suppression (HBV DNA <3 $\log_{10}$ copies/mL on 2 consecutive visits or at the last visit) was different from that of the Applicant (HBV DNA <5 $\log_{10}$ copies/mL on 2 consecutive visits or at the last visit). The 1,000 copies/mL cutoff was chosen because this level was previously used for the resistance analysis in the adefovir and entecavir NDAs. The percentage of patients with virologic failure in Table 11 of the microbiology review was approximately 100 minus the percentage of patients with HBV DNA levels < 3 log10 copies/mL at Week 52 in Table 11-31 of the Clinical Study Report.

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HBsAg loss was defined as:

- **loss of detectable serum HBsAg**
- **in a patient with detectable HBsAg at Baseline**

HBsAg seroconversion was defined as:

- **HBsAg loss with detectable HBsAb**

HBsg loss and seroconversion at weeks 24 and 52 using denominators from the primary analysis – HBeAG+, ITT population

	HBeAg-positive		HBeAg-negative	
	Lamivudine n/N (%)	Telbivudine n/N (%)	Lamivudine n/N (%)	Telbivudine n/N (%)
HBsAg loss				
Week 52	6/458 (1.3)	3/452 (0.7)	2/224 (0.9%)	1/222 (0.5%)
HBsAg seroconversion				
Week 52	2/458 (0.4)	0/452	2/224 (0.9%)	1/222 (0.5%)

Source: Tables 14.2.1.3 and 14.2.1.5 of the Clinical Study Report
Non-inferiority Margin was not pre-specified. Only superiority testing was pre-specified.

Very low response rates were observed for HBsAg loss and HBsAg seroconversion and no statistically significant treatment differences were detected because these responses were only expected to occur months to years after HBeAg loss.

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Key efficacy results at Week 52, by treatment, in HBeAg-positive ITT population with Baseline ALT >/= 2xULN ("interferon eligible" population)

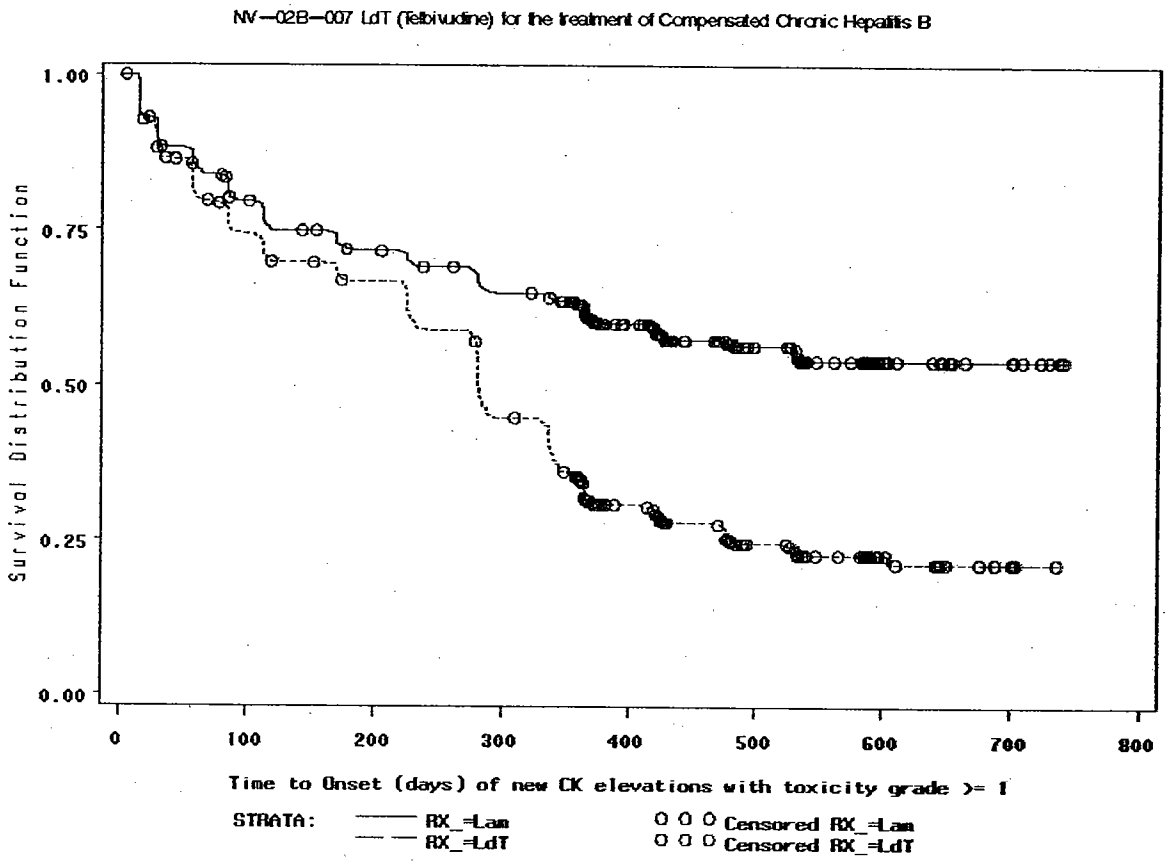
	HBeAg-positive, ALT ≥ 2xULN		p-value=
	Lamivudine (N=309)	Telbivudine (N=305)	
Therapeutic Response	73.2%	80.3%	0.0319
Histologic Response	60.8%	69.2%	0.0281
HBV DNA decrease	-5.84 log10	-6.60 log10	0.0001
PCR-nondetectable	46.4%	69.1%	0.0000
ALT normalization	77.5%	81.2%	0.2621
Viral Breakthrough	11.0%	3.6%	0.0004
HBV resistance	9.0%	3.3%	0.0033
Virologic Response	25.9%	32.2%	0.0846
HBeAg seroconversion	24.3%	28.2%	0.2644
HBeAg loss	26.5%	32.2%	0.1237
Treatment Failure	10.1%	2.0%	0.0000

Source: Table 11-41 of the Clinical Study Report

In Table 11-41 of the Clinical Study Report, Idenix summarized key efficacy results at Week 52, by treatment, with baseline ALT $\geq 2 \times$ ULN in the "interferon eligible" HBeAg-positive ITT population which represented only 614/921 = 66.7% or two-thirds of the HBeAg-positive ITT population enrolled in this study. According to the sponsor this is the population that has been studied in most trials of interferon therapy and corresponds to a population recommended for treatment in the current AASLD and APASL guidelines.

As in the all HBeAg-positive ITT patients, statistical significance was demonstrated for the first four endpoints (therapeutic response, histologic response, HBV DNA decrease and PCR-nondetectable). There were also statistically significant treatment differences for some of the remaining secondary efficacy parameters, but since there was no statistically significant treatment difference for ALT normalization, all subsequent hierarchical tests could not be used to declare that telbivudine was superior to lamivudine. (The results of these tests appear on the rows below the row corresponding to ALT normalization.)

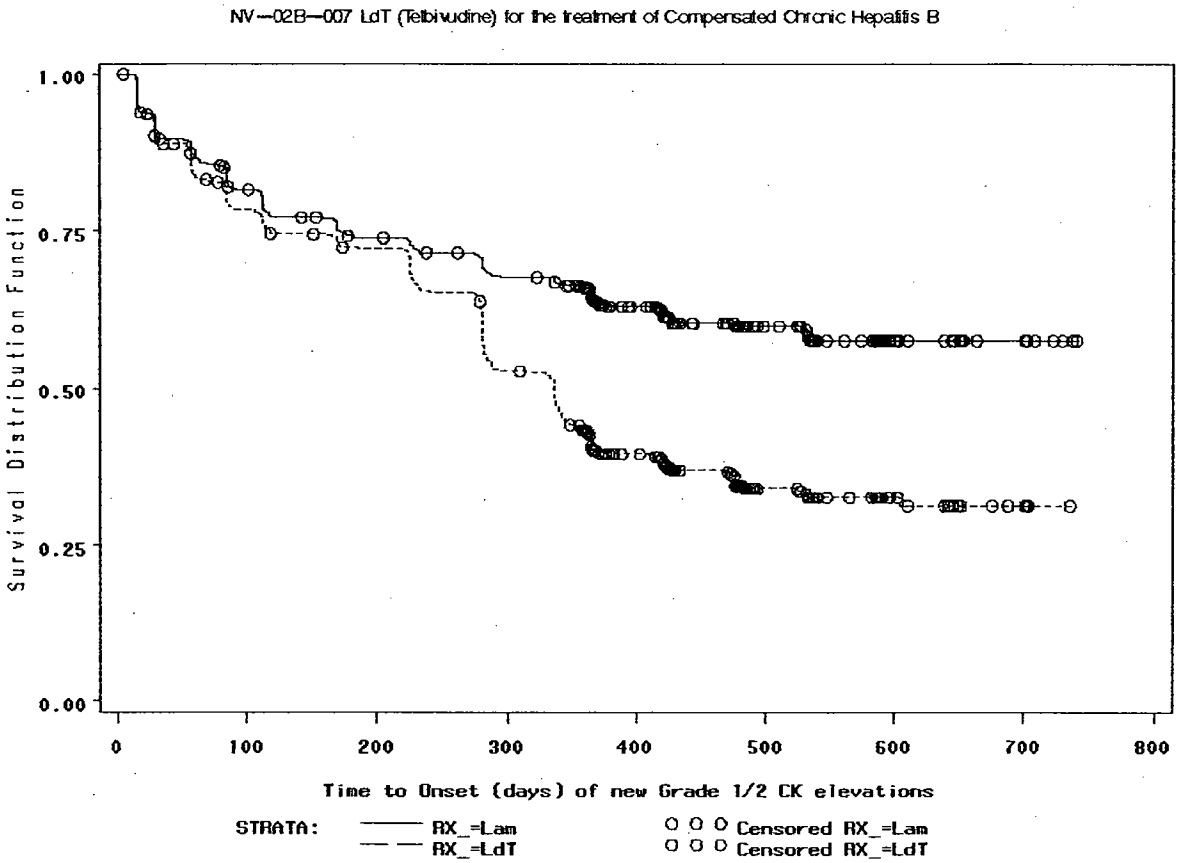
3.2 Evaluation of Safety



Source: Statistical Reviewer's Analysis

Compared to lamivudine, the percentage of patients with new CK elevations with toxicity grade ≥ 1 was significantly higher in telbivudine patients; 488/680 (72%) of telbivudine patients had new CK elevations with toxicity grade ≥ 1 compared to only 285/687 (41%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

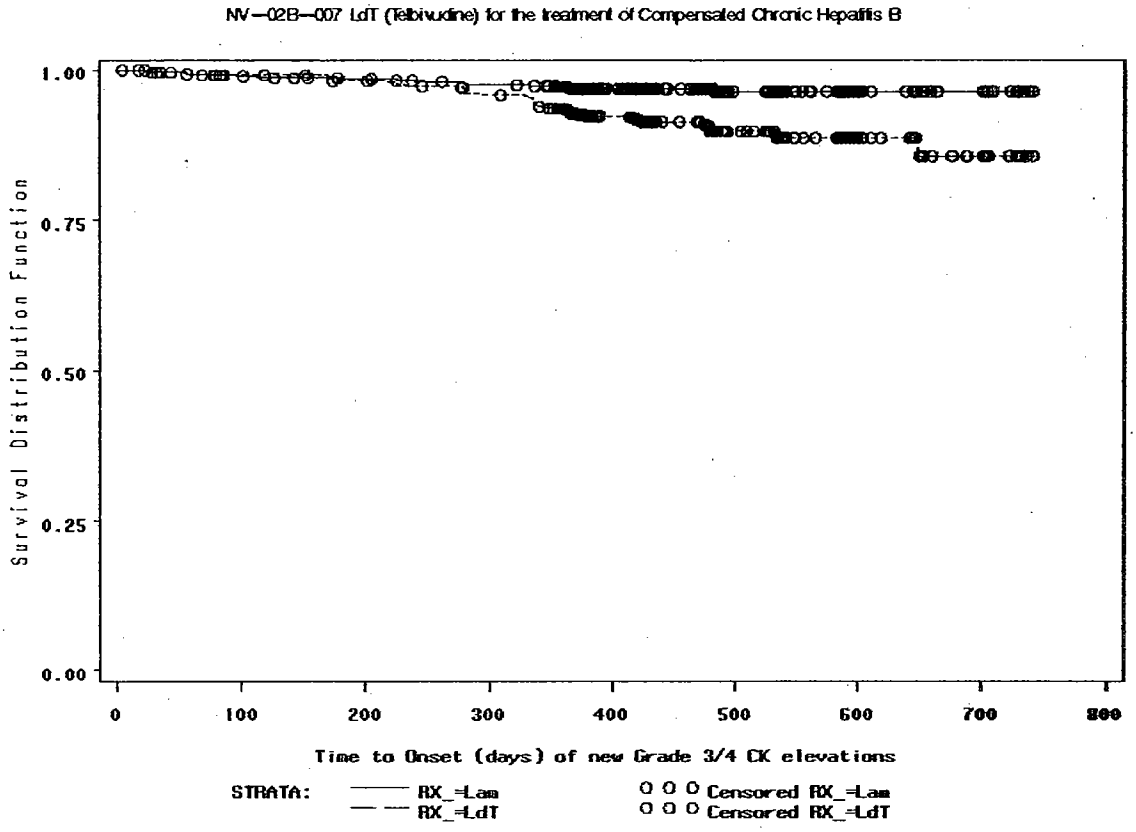
The Kaplan-Meier plot of time to onset of new CK elevations with toxicity grade ≥ 1 also shows a much higher incidence of events in telbivudine subjects (25 percentile = only 87 days for telbivudine compared to 117 days for lamivudine; $p<0.001$ using the log rank test).



Source: Statistical Reviewer's Analysis

Compared to lamivudine, the percentage of patients whose worst laboratory toxicity grade was 1 or 2 during the period was significantly higher in telbivudine patients; 427/680 (63%) of telbivudine patients had new grade 1/2 CK elevations compared to only 263/687 (38%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

The Kaplan-Meier plot of time to onset of new grade 1/2 CK elevations also shows a much higher incidence of events in telbivudine subjects (25 percentile = only 119 days for telbivudine compared to 171 days for lamivudine; $p<0.001$ using the log rank test).



Source: Statistical Reviewer's Analysis

Compared to lamivudine, the percentage of patients with new grade 3/4 CK elevations was significantly higher in telbivudine patients; 61/680 (9%) of telbivudine patients had new grade 3/4 CK elevations compared to only 22/687 (3%) **of lamivudine patients ($p<0.001$ using Fisher's** Exact test).

The Kaplan-Meier plot of time to onset of new grade 3/4 CK elevations also shows a much higher incidence of events in telbivudine subjects ($p<0.001$ using the log rank test).

***NV-02B-007*: Summary of Number (and percentage) of patients with CK elevations On Treatment who recovered on or off treatment**

Toxicity Grade	Treatment	Number (%) of CK Elevations	Number (%) who Recovered	Mean Recovery Time (Days)[1]	Median Recovery Time (Days)[1]
1-4	LdT	488/680=72%	208/488=43%	183	131
	Lamivudine	285/687=41%	208/285=73%	164	64
1-2[2]	LdT	427/680=63%	191/427=45%	174	106
	Lamivudine	263/687=38%	199/263=76%	156	63
3-4	LdT	61/680=9%	51/61=84%	58	36
	Lamivudine	22/687=3%	20/22=91%	46	29

Source: Statistical Reviewer's Analysis
[1] Mean and Median Recovery Time computed for patients who recovered from CK elevations
[2] Only patients whose worst laboratory toxicity grade is 1 or 2 during the period are included

The percentage of patients with CK elevations who recovered and corresponding time to recovery among patients who recovered were also summarized by the statistical reviewer. Recovery was defined as a final CK measurement below the upper limit of normal or below the given toxicity grade. Time to recovery was defined as the time it took after a CK elevation to observe the first CK measurement and all subsequent CK measurements to be below the upper limit of normal or below the given toxicity grade.

On page 182 of the clinical study report, the applicant claimed that CK elevations were brief and didn't require treatment discontinuation. However, compared to lamivudine, a smaller percentage of patients randomized to LdT recovered from CK elevations and recovery from CK elevations took longer in LdT patients.

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***NV-02B-007*: Summary of On-Treatment ALT Flare Phenomena (patients are only counted as being in their worst category)**

ALT Flare Category, n (%)	HBeAg-Positive		HBeAg-Negative		Total	
	LdT (n=445)	LAM (n=455)	LdT (n=235)	LAM (n=232)	LdT (n=680)	LAM (n=687)
ALT Flare Category 1	36 (8)	33 (7)	5 (2)	6 (3)	41 (6)	39 (6)
ALT Flare Category 2	16 (4)	18 (4)	0	9 (4)	16 (2)	27 (4)
ALT Flare Category 3	16 (4)	26 (6)	2 (1)	3 (1)	18 (3)	29 (4)
ALT Flare Category 4	0	3 (1)	0	0	3 (0.4)	0

Source: Statistical Reviewer's Analysis

The four categories of ALT flares (in order of severity) were:

1. ALT $\geq 2 \times$ Baseline and $\geq 2 \times$ ULN
2. ALT $\geq 3 \times$ Baseline and $\geq 3 \times$ ULN
3. ALT $\geq$ 500 IU/L and $\geq 2 \times$ Baseline
4. ALT $\geq 2 \times$ Baseline and Bilirubin $\geq 2 \times$ Baseline and ALT $\geq 2 \times$ ULN and Bilirubin $\geq 2 \times$ ULN

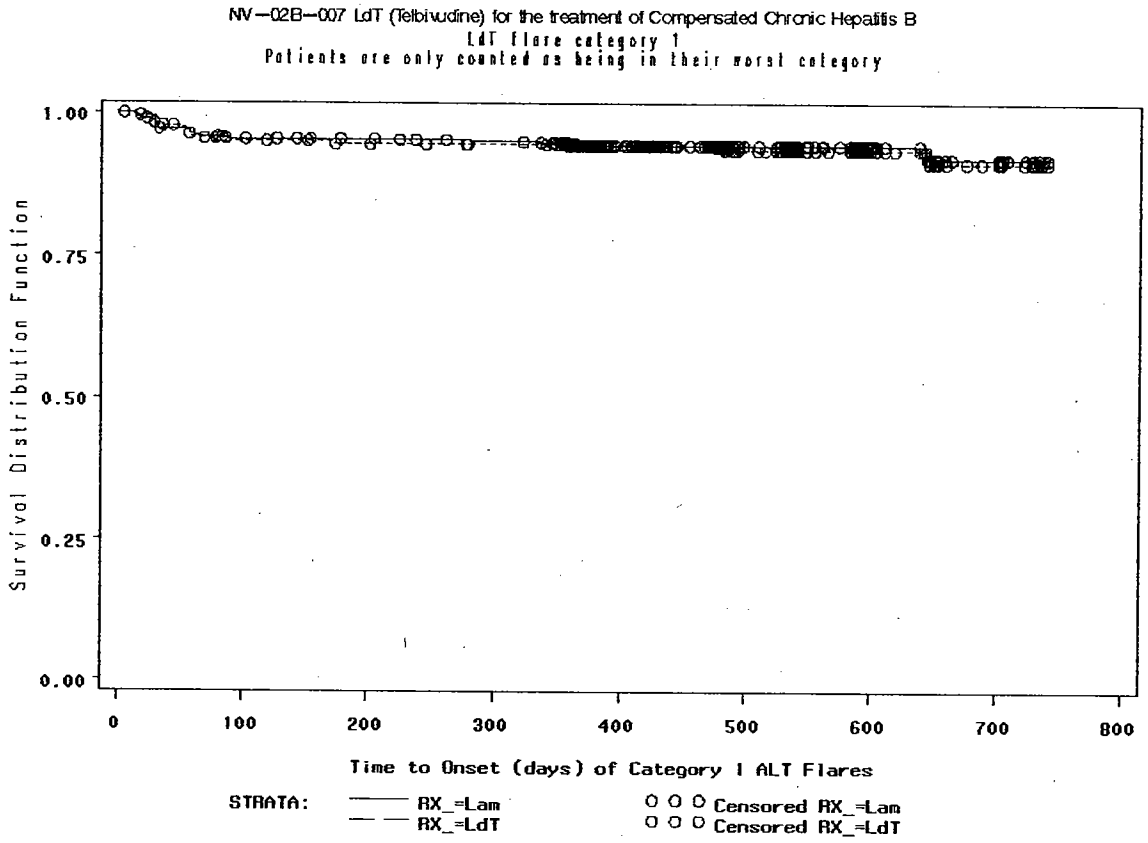
There were no statistically significant differences between the proportions of patients in each treatment group with ALT flares.

NV-02B-007*: Summary of On-Treatment ALT Flare Phenomena using AASLD Criteria *(ALT > 2 × BL and ALT > 10 × ULN)

ALT Flare, n (%)	HBeAg Positive		HBeAg Negative		Total	
	LdT (n=445)	LAM (n=455)	LdT (n=235)	LAM (n=232)	LdT (n=680)	LAM (n=687)
AASLD Flares	20 (4)	32 (7)	2 (1)	3 (1)	22 (3)	35 (5)

Source: Statistical Reviewer's Analysis

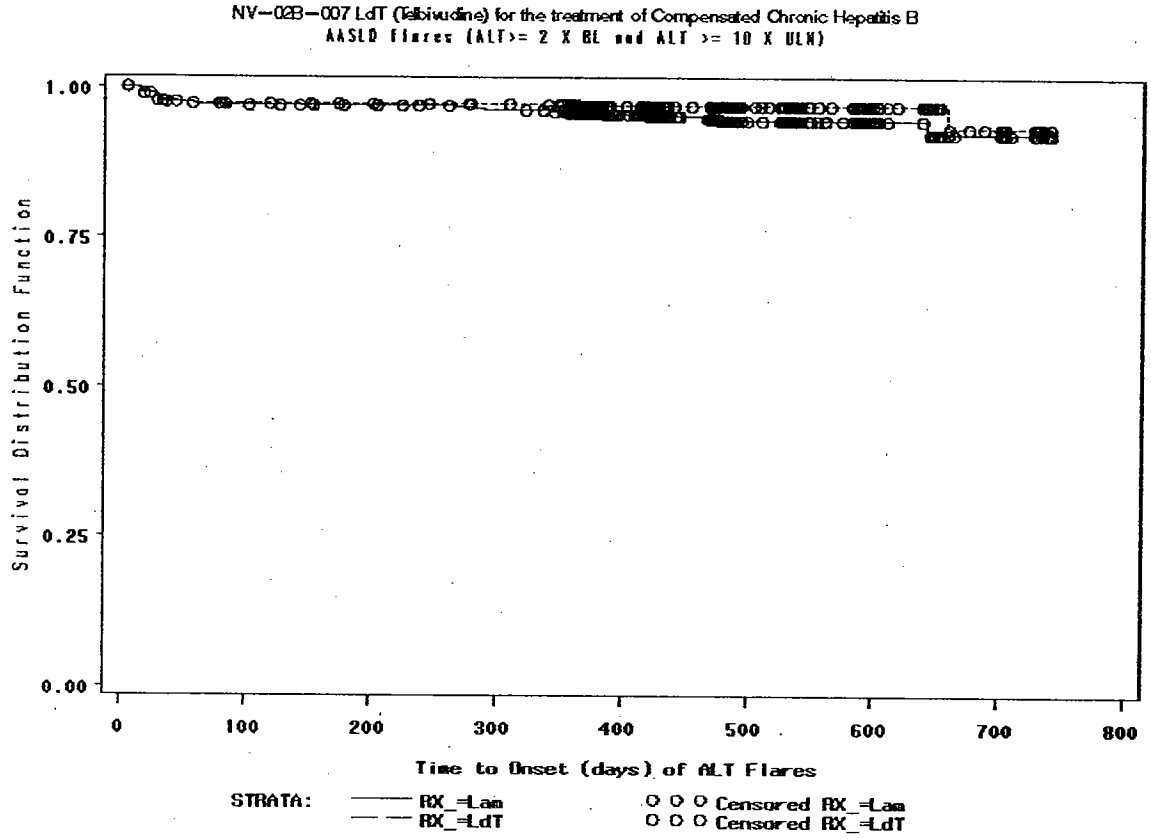
Using American Association for the Study of Liver Diseases (AASLD) criteria, there were no statistically significant differences between the proportions of patients with ALT flares in each treatment group (p=0.12 in the HBeAg-positive subpopulation, p=0.68 in the HBeAg-negative subpopulation, and p=0.09 for the combined HBeAg-stratified CMH analysis for all patients).



Source: Statistical Reviewer's Analysis

The Kaplan-Meier plot of time to onset of Category 1 ALT Flares also shows a similar percentage of ALT flares in LdT and lamivudine treatment groups.

(Kaplan-Meier plots of Category 2-4 ALT Flares did not provide any additional useful information because of the small percentage of events in each category.)



Source: Statistical Reviewer's Analysis

Using AASLD criteria there was no statistically significant difference between the proportion of patients in each treatment group with ALT flares although the p-value (0.09) was small enough to be indicative of a possible trend favoring lamivudine over LdT.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Therapeutic Response at Week 52 by treatment and gender
HBeAg+ and HBeAg- populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
HBeAg-positive				
Male	228/351 (65)	241/333 (72)	1, 14	0.03
Female	82/112 (73)	104/125 (83)	-1, 20	0.07
HBeAg-negative				
Male	137/178 (77)	134/174 (77)	-9, 9	0.995
Female	36/46 (78)	33/48 (69)	-28, 9	0.32

Source: Tables 14.2.1.15 and 14.2.1.16 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.
Non-inferiority Margin=-15%

Non-inferiority of telbivudine to lamivudine was demonstrated in males in both HBeAg subpopulations and in females in the HBeAg-positive subpopulation. Ldt was not observed to be non-inferiority to lamivudine in females in the HBeAg-negative subpopulation.

The superiority of telbivudine over lamivudine was only demonstrated in males in the HBeAg-positive subpopulation. There were no statistically significant treatment effects in favor of lamivudine.

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Therapeutic Response at Week 52 by treatment and race - HBeAg+ and HBeAg- populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
HBeAg-positive				
Asian	261/371 (70)	299/380 (79)	2, 14	0.0085
Caucasian	30/55 (55)	31/52 (60)	-14.6, 23	0.67
Other	19/37 (51)	15/26 (58)	-11, 13	0.30
HBeAg-negative				
Asian	117/144 (81)	117/145 (81)	-10, 8	0.88
Caucasian	44/56 (79)	29/46 (63)	-33, 2	0.08
Other	12/24 (50)	21/31 (68)	-8, 44	0.18

Source: Tables 14.2.1.18 and 14.2.1.19 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.
Non-inferiority Margin=-15%

Non-inferiority of telbivudine to lamivudine was demonstrated in Asians and Other Races in both HBeAg subpopulations and Caucasians who were HBeAg-positive. The superiority of telbivudine over lamivudine was only demonstrated in Asians in the HBeAg-positive subpopulation. There were no statistically significant treatment effects in favor of lamivudine.

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Therapeutic Response at Week 52 by treatment and age - HBeAg+ and HBeAg- populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
HBeAg-positive				
Age < 30 years	130/208 (62)	177/224 (79)	9, 26	<0.001
Age 30-50 years	150/214 (71)	145/205 (70)	-9, 8	0.94
Age > 50 years	30/41 (75)	23/29 (79)	-17, 24	0.74
HBeAg-negative				
Age < 30 years	25/30 (83)	29/32 (91)	-9, 24	0.39
Age 30-50 years	104/135 (77)	104/132 (79)	-8, 12	0.73
Age > 50 years	44/59 (75)	34/58 (59)	-33, 1	0.07

Source: Tables 14.2.1.12 and 14.2.1.13 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.
Non-inferiority Margin=-15%

Non-inferiority of telbivudine to lamivudine was demonstrated in ages <30 years and 30-50 years in both HBeAg subpopulations. The superiority of telbivudine over lamivudine was only demonstrated in the <30 year olds in the HBeAg-positive subpopulation. Non-inferiority was not observed for telbivudine in patients >50 years of age. There were no statistically significant treatment group differences in favor of lamivudine in any of the subgroup analyses.

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4.1 Other Special/Subgroup Populations

Therapeutic Response at Week 52 by treatment and randomization stratum - ITT and EE populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
ITT population				
HBeAg+/ALT <2.5 x ULN	123/217 (56.7)	147/212 (69.3)	3.6, 21.7	0.0061
HBeAg+/ALT ≥2.5 x ULN	187/246 (76.0)	198/246 (80.5)	-2.8, 11.8	0.2286
HBeAg-/ALT <2.5 x ULN	82/112 (73.2)	84/111 (75.7)	-9.0, 13.9	0.6734
HBeAg-/ALT ≥2.5 x ULN	91/112 (81.3)	83/111 (74.8)	-17.3, 4.4	0.2417
EE population				
HBeAg+/ALT <2.5 x ULN	109/201 (54.2)	139/200 (69.5)	5.9, 24.7	0.0014
HBeAg+/ALT ≥2.5 x ULN	190/244 (77.9)	195/234 (83.3)	-1.6, 12.5	0.1296
HBeAg-/ALT <2.5 x ULN	87/114 (76.3)	86/113 (76.1)	-11.3, 10.9	0.9704
HBeAg-/ALT ≥2.5 x ULN	93/109 (85.3)	88/115 (76.5)	-19.0, 1.4	0.0910

Source: Table 11-22 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.
Breslow-Day p-value =0.11 for test of homogeneity of treatment effect in the 4 HBeAG / ALT strata in the ITT population.
Non-inferiority Margin=-15%

Non-inferiority of telbivudine to lamivudine was demonstrated in the HBeAg-Positive subpopulation in both ALT strata and in the HBeAg-Negative subpopulation in patients with baseline ALT <2.5 × ULN. The superiority of telbivudine over lamivudine was demonstrated in the HBeAg-positive subpopulation among patients with baseline ALT < 2.5 × ULN. There were no statistically significant treatment group differences in favor of lamivudine in any of the subgroup analyses.

Therapeutic Response at Week 52 by treatment and genotype - HBeAg+ and HBeAg- populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
HBeAg-positive				
Genotype B	81/113 (71)	99/129 (77)	-5, 17	0.31
Genotype C	180/258 (70)	205/259 (79)	2, 16	0.02
Other	49/92 (53)	41/70 (59)	-9, 21	0.42
HBeAg-negative				
Genotype B	48/59 (81)	47/59 (80)	-16, 13	0.83
Genotype C	67/86 (78)	72/89 (81)	-9, 15	0.65
Other	58/79 (74)	48/73 (66)	-22, 7	0.30

Source: Tables 14.2.1.21 and 14.2.1.22 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.
Non-inferiority Margin=-15%

Non-inferiority of telbivudine to lamivudine was demonstrated in the three genotype subgroups in the HBeAg-positive subpopulation and in the genotype C subgroup in the HBeAg-negative subpopulation. The superiority of telbivudine over lamivudine was demonstrated in the genotype C subgroup in the HBeAg-positive subpopulation. There were no statistically significant treatment group differences in favor of lamivudine in any of the subgroup analyses.

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Therapeutic Response at Week 52 by treatment and baseline HBV DNA - HBeAg+ and HBeAg- populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
HBeAg-positive				
< 1st tertile	75/96 (78)	71/85 (84)	-6, 17	0.35
1st – 2nd tertile	36/52 (70)	54/68 (79)	-7, 25	0.25
>2nd tertile	112/207 (54)	128/193 (66)	3, 22	0.009
HBeAg-negative				
< 1st tertile	125/156 (80)	103/136 (76)	-14, 6	0.40
1st – 2nd tertile	37/53 (70)	44/58 (76)	-10, 23	0.45
>2nd tertile	11/15 (74)	20/28 (71)	-30, 24	0.82

Source: Tables 14.2.1.21 and 14.2.1.22 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.
Non-inferiority Margin=-15%

Non-inferiority of telbivudine to lamivudine was demonstrated in the three baseline HBV DNA subgroups in the HBeAg-positive subpopulation and in the <1st and 1st-2nd tertiles in the HBeAg-negative subpopulation. The superiority of telbivudine over lamivudine was demonstrated in the >2nd tertile in the HBeAg-positive subpopulation. There were no statistically significant treatment group differences in favor of lamivudine in any of the subgroup analyses.

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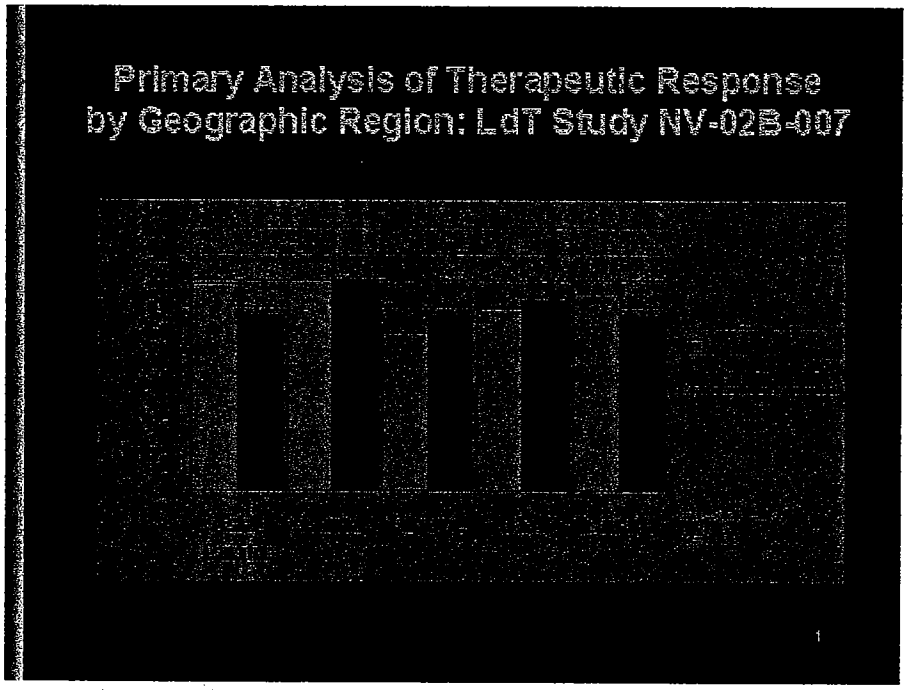

Source: Statistical Reviewer's Analysis

Therapeutic responses were examined in different geographic regions. LdT appeared to have the most impressive treatment effect (compared to lamivudine) in the Asia-Pacific region and Canada.

The Breslow-Day for testing the homogeneity of treatment effects by geographic region was 0.06, which was not statistically significant but small enough to be indicative of a possible treatment by geographic region interaction.

Therapeutic Response at Week 52 by treatment and geographic region - HBeAg+ and HBeAg- populations

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	p-value
HBeAg+ population				
Asia	243/350 (69)	280/355 (79)	3, 16	0.003
North America	39/59 (66)	33/48 (69)	-15.3, 20	0.78
Other	28/54 (52)	32/55 (58)	-12, 25	0.51
HBeAg- population				
Asian	105/139 (76)	121/154 (79)	-7, 12	0.62
North America	24/31 (79)	20/26 (75)	-26, 18	0.74
Other	44/54 (82)	26/42 (62)	-38, -2	0.03

Source: Tables 14.2.1.24 and 14.2.1.25 of the Clinical Study Report
Treatment group differences controlled for randomization strata: difference between proportions.

Telbivudine was non-inferior to lamivudine in Asians in both HBeAg subpopulations and non-inferior in Europe (other geographic regions outside Asia and North America) in the HBeAg-positive subpopulation.

Treatment differences were also statistically significant (p=0003) in favor of telbivudine for the HBeAg-positive subpopulation in Asia and marginally significant (p=0.03) in favor of lamivudine for the HBeAg-negative subpopulation in Europe.

The four sites that the Division of Scientific Investigations (DSI) inspected (008, 050, 057, 041) were all in the Asia-Pacific region and each of these sites had more LdT therapeutic responders than lamivudine:
At Site 008 in Taiwan, 29/33=88% of the LdT subjects had a therapeutic response compared to 20/26=77% of the lamivudine controls.
At Site 050 in Thailand, 21/24=88% of the LdT subjects had a therapeutic response compared to 16/27=59% of the lamivudine controls.
At Site 057 in New Zealand, 25/35=71% of the LdT subjects had a therapeutic response compared to 20/31=65% of the lamivudine controls.
At Site 041 in Australia, 4/5=80% of the LdT subjects had a therapeutic response compared to 11/17=65% of the lamivudine controls.

Other Asian sites with a large pool of patients included:
Site 003 in Hong Kong, where 26/38=68% of the LdT subjects had a therapeutic response compared to 20/32=63% of the lamivudine controls.
Site 108 in China, where 20/26=77% of the LdT subjects had a therapeutic response compared to 16/25=64% of the lamivudine controls.

Site 054 in Korea had a very favorable LdT response compared to lamivudine, where nearly all of the LdT subjects had a therapeutic response (17/18=94%) compared to only 3/8=38% of the lamivudine controls but this site was relatively small compared to some of the other Asian sites previously mentioned.

Other smaller Asian sites with favorable LdT treatment effects included:

Site 012 in Singapore, where 16/17=94% of the LdT subjects had a therapeutic response compared to 8/13=62% of the lamivudine controls.
Site 007 in Taiwan, where 8/10=80% of the LdT subjects had a therapeutic response compared to 8/16=50% of the lamivudine controls.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Clinical and virologic efficacy endpoints were evaluated separately in the HBeAg-positive and HBeAg-negative subject populations in Study 007.

Histological Improvement and Change in Ishak Fibrosis Score at Week 52 (007 GLOBE Study)

	HBeAg-positive (n =797)		HBeAg-negative (n =417)	
	Telbivudine 600 mg (n=399)[1]	**Lamivudine 100 mg (n=398)[1]**	**Telbivudine 600 mg (n=205)[1]**	**Lamivudine 100 mg (n=212)[1]**
Histologic Response [2]				
Improvement	69%	60%	69%	68%
No Improvement	19%	26%	23%	25%
Missing Week 52 Biopsy	12%	15%	8%	7%
Ishak Fibrosis Score[3]				
Improvement	41%	46%	48%	44%
No Change	39%	32%	34%	43%
Worsening	9%	7%	10%	5%
Missing Week 52 Biopsy	12%	15%	8%	7%

[1] Patients with ≥ one dose of study drug with evaluable baseline liver biopsies and baseline Knodell Necroinflammatory Score ≥ 2

[2] Histologic Response defined as ≥2 point decrease in Knodell Necroinflammatory Score from baseline with no worsening of the Knodell Fibrosis Score

[3] For Ishak Fibrosis Score, improvement defined as a ≥ 1-point reduction in Ishak fibrosis score from Baseline to Week 52

Source: Table 2 from the Telbivudine label

Compared to lamivudine patients, a significantly greater proportion of telbivudine patients in the HBeAg-positive subpopulation experienced a histologic response at Week 52. Non-inferiority was demonstrated for telbivudine in the HBeAg-negative population.

Change in Ishak Fibrosis Score for telbivudine did not meet the pre-specified non-inferioritiy criterion (lower limit of the 95% confidence interval > -8%) for HBeAg-positive patients. In

addition, the p-value for the difference between telbivudine and lamivudine in the HBeAg-positive subpopulation was almost statistically significant in favor of lamivudine. There was no statistically significant treatment difference in the HBeAg-negative subpopulation.

The primary efficacy endpoint for the phase III study was the proportion of randomized patients with a Therapeutic Response which was defined as:

- Serum HBV DNA suppression < 5 $\log_{10}$ copies/mL at Week 52

AND

- HbeAg loss at Week 52 or ALT normalized at Week 52

HBeAg loss at Week 52 was defined as loss of detectable serum HBeAg at Week 52 in a patient who was HBeAg+ at Baseline

ALT normalized at Week 52 was defined as ALT within normal limits at Week 52 for a patient with an elevated Alt level (> 1.0 × ULN) at either Baseline or Screening

Compared to lamivudine patients, a significantly greater proportion of telbivudine patients in the HBeAg-positive subpopulation experienced a therapeutic response; 67% of the lamivudine subjects and 75% of the telbivudine subjects had a therapeutic response at Week 52 in the ITT population.

Non-inferiority was demonstrated for telbivudine in the HBeAg-negative population where 77% of the lamivudine subjects and 75% of the telbivudine subjects had a therapeutic response at Week 52 in the ITT population.

Corrections to the applicant's conclusions are noted in the table below summarizing hierarchical fixed hypothesis testing results for primary and secondary endpoints in study NV-02B-007.

Results of hierarchical fixed hypothesis testing of primary and secondary efficacy endpoints

Efficacy Endpoint*		Subpopulations	
		HBeAg-positive	HBeAg-negative
1	Therapeutic Response	S	NI
2.1	Histologic Response	S	NI
2.2	Serum HBV DNA Reduction	S	~~S~~[1] NI
2.3	Serum HBV DNA Undetectable	S	~~S~~[1] NI
2.4	ALT Normalization	NI	NI
2.5	Virologic Breakthrough at Week 48	~~S~~[1] NI	~~S~~[1] NI
2.6	Virologic Response	NI	/
2.7	HBeAg Seroconversion	NI	/
2.8	HBeAg Loss	NI	/
2.9	Change in Ishak Fibrosis Score	~~NI~~[2]	NI
2.10	Primary Treatment Failure	~~S~~[1]	Unable to achieve superiority
2.11	HBsAg Loss	~~NI~~[3]	/
2.12	HBsAg Seroconversion	~~NI~~[3]	/

Source: Table 11-20 in the Clinical Study Report
*All Endpoints are for Week 52 unless otherwise specified.
Note: S = Superiority
NI = Non-Inferiority
/ = Not Applicable.
[1] Superiority for the current test (e.g., 2.5) cannot be demonstrated because previous test (e.g., 2.4) did not demonstrate superiority
[2] Failed to demonstrate non-inferiority (see Table 11-28)
[3] Only a small percentage had HBsAg loss of in the first year of treatment and the statistical analysis plan stated that there would be no non-inferiority test for this endpoint.

Based on our review of the collective data we conclude the following.

1. LdT was superior to lamivudine in the HBeAg-positive subpopulation and non-inferior to lamivudine in the HBeAg-negative subpopulation for the following endpoints: Therapeutic Response (primary endpoint), Histologic Response (Key Secondary Endpoint), Serum HBV DNA Reduction, and Serum HBV DNA Undetectable.

2. LdT was non-inferior to lamivudine in both HBeAg subpopulations for ALT Normalization and Virologic Breakthrough at Week 48.

3. LdT was also non-inferior to lamivudine in the HBeAg-positive subpopulation for Virologic Response, HBeAg Seroconversion and HBeAg Loss.

4. The study failed to demonstrate that LdT was non-inferiority to lamivudine for change in Ishak Fibrosis Score in the HBeAg-positive subpopulation and the treatment difference was almost statistically significant in favor of lamivudine.

The applicant cannot claim superiority for any secondary endpoints in the hierarchy if LdT was not superior to lamivudine for any previous endpoints. For example, in the HBeAg-negative subpopulation, LdT is not superior to lamivudine for Serum HBV DNA Reduction or Serum HBV DNA Undetectable because LdT was not superior to lamivudine for the therapeutic response or the histologic response endpoints. Corrections by the statistical reviewer are indicated by crossing a line through the applicant's claim of NI or S and providing reasons in footnotes.

In the HBeAg-positive subpopulation, since Virologic Breakthrough at Week 48 and Primary Treatment Failure were after ALT Normalization in the hierarchy of fixed hypothesis testing, and telbivudine was not shown to be superior to lamivudine with respect to ALT normalization, it is not valid to claim that telbivudine is superior to lamivudine for Virologic Breakthrough or Primary Treatment Failure.

Non-inferiority of telbivudine to lamivudine can be claimed for Virologic Breakthrough at Week 48 in the HBeAg-positive subpopulation even though a non-inferiority margin was not pre-specified because there was a statistically significant difference in favor of LdT for this endpoint (i.e., the lower bound of the confidence interval was greater than 0, the smallest possible non-inferiority margin).

Non-inferiority of telbivudine to lamivudine cannot be claimed for Primary Treatment Failure in the HBeAg-positive subpopulation because non-inferiority for Change in Ishak Fibrosis Score was not achieved previously in the hierarchical testing procedure. There was no statistically significant difference between telbivudine and lamivudine for primary treatment failure in the HBeAg-negative subpopulation.

The DAVP does not intend to grant Idenix a claim in the label of superiority of LdT over lamivudine for the Therapeutic Response, Histologic Response, Serum HBV DNA Reduction or Serum HBV DNA Undetectable endpoints within the HBeAg-positive subpopulation without replication in a future study in this subpopulation.

However in the statistical review we will determine whether LdT is superior to lamivudine for a given endpoint in study NV-02B-007 only based upon the hierarchical fixed hypotheses that were pre-specified in the SAP.

Compared to lamivudine, the percentage of patients with new CK elevations with toxicity grade ≥ 1 was significantly higher in telbivudine patients; 488/680 (72%) of telbivudine patients had new CK elevations with toxicity grade ≥ 1 compared to only 285/687 (41%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

Compared to lamivudine, the percentage of patients whose worst CK toxicity grade was 1 or 2 during the period was significantly higher in telbivudine patients; 427/680 (63%) of telbivudine patients had new grade 1/2 CK elevations compared to only 263/687 (38%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

Compared to lamivudine, the percentage of patients with new grade 3/4 CK elevations was significantly higher in telbivudine patients; 61/680 (9%) of telbivudine patients had new grade 3/4 CK elevations compared to only 22/687 (3%) of lamivudine patients ($p<0.001$ using Fisher's Exact test).

***NV-02B-007*: Summary of Number (and percentage) of patients with CK elevations On Treatment who recovered on or off treatment**

Toxicity Grade	Treatment	Number (%) of CK Elevations	Number (%) who Recovered	Mean Recovery Time (Days)[1]	Median Recovery Time (Days)[1]
1-4	LdT	488/680=72%	208/488=43%	183	131
	Lamivudine	285/687=41%	208/285=73%	164	64
1-2[2]	LdT	427/680=63%	191/427=45%	174	106
	Lamivudine	263/687=38%	199/263=76%	156	63
3-4	LdT	61/680=9%	51/61=84%	58	36
	Lamivudine	22/687=3%	20/22=91%	46	29

Source: Statistical Reviewer's Analysis
[1] Mean and Median Recovery Time computed for patients who recovered from CK elevations
[2] Only patients whose worst laboratory toxicity grade is 1 or 2 during the period are included

The percentage of patients with CK elevations who recovered and corresponding time to recovery among patients who recovered were also summarized by the statistical reviewer. Recovery was defined as a final CK measurement below the upper limit of normal or below the given toxicity grade. Time to recovery was defined as the time it took after a CK elevation to observe the first CK measurement and all subsequent CK measurements to be below the upper limit of normal or below the given toxicity grade.

On page 182 of the clinical study report, the applicant claimed that CK elevations were brief and didn't require treatment discontinuation. However, compared to lamivudine, a smaller percentage of patients randomized to LdT recovered from CK elevations and recovery from CK elevations took longer in LdT patients.

5.2 Conclusions and Recommendations

There was one pivotal double-blind, randomized, controlled phase III clinical study included in this application to support the use of telbivudine (LdT) to treat adults with compensated chronic hepatitis B.

The non-inferiority of telbivudine to lamivudine was established in both HBeAg subpopulations for Therapeutic Response (the primary endpoint), Histologic Response, (the primary secondary endpoint), Serum HBV DNA Reduction, Serum HBV DNA Undetectable, ALT Normalization and Virologic Breakthrough at Week 48.

Non-inferiority of telbivudine to lamivudine was also demonstrated in the HBeAg-positive subpopulation for Virologic Response, HBeAg seroconversion and HBeAg Loss and in the HBeAg-negative subpopulation for Change in Ishak Fibrosis Score.

According to the statistical testing procedure pre-specified in the statistical analysis plan, the superiority of telbivudine over lamivudine was also demonstrated in the HBeAg-positive subpopulation for the Therapeutic Response, Histologic Response, Serum HBV DNA Reduction and Serum HBV DNA Undetectable. However since superiority for the same endpoints was not demonstrated in the HBeAg-negative subpopulation, the Division of Antiviral Products (DAVP) will require replication of the superiority findings in the HBeAg-positive subgroup in another study before allowing Idenix to make this claim in the label.

Change in Ishak Fibrosis Score for telbivudine did not meet the pre-specified non-inferioritiy criterion for the HBeAg-positive subpopulation and the p-value for the difference between telbivudine and lamivudine was almost statistically significant in favor of lamivudine.

Creatine kinase (CK) elevations were more frequent among subjects on telbivudine treatment. Grade 3/4 CK elevations occurred in 9% of telbivudine-treated patients and 3% of lamivudine-treated patients. Most CK elevations were asymptomatic but the recovery time was longer for subjects on telbivudine than subjects on lamivudine.

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/s/

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