5.3.2 Study NV-02B-015

Title: A phase 3 randomized, double-blind trial of LdT (telbivudine) versus lamivudine in Chinese adults with compensated hepatitis B

Study Objectives: To compare efficacy and safety of telbivudine and lamivudine in adults with chronic hepatitis B (HBeAg-positive and HBeAg-negative) over two years.

Primary Endpoint: Serum HBV Reduction from baseline at Week 52

Key Secondary Endpoint: Therapeutic Response at Week 52

Medical Officer Comments: *Note that assessment of histologic response was not evaluated as an outcome measure in this study. At this time, DAVP requires determination of a histologic outcome to confirm efficacy determined by surrogate markers (HBV DNA, ALT, serologic response).*

Other Secondary Endpoints:
The following table describes the multiple secondary endpoints assessed in this study.

Table 55. Definitions for Efficacy Endpoints

Table 9-7 Definitions of categorical efficacy endpoints

Endpoint	Definition
Therapeutic Response (HBeAg-positive patients only)	Serum HBV DNA <5 $\log_{10}$ copies/mL and either HBeAg loss or ALT normalization.
Composite Serologic Response (Therapeutic Response for HBeAg-negative patients only)	Serum HBV DNA <5 $\log_{10}$ copies/mL and ALT normalization.
HBV DNA suppression	In patients with ≥6 $\log_{10}$ copies/mL at Baseline, serum HBV DNA <5 $\log_{10}$ copies/mL on 2 consecutive visits or at the last visit*.
HBV DNA PCR negative	HBV DNA below LLOQ (<300 copies/mL).
ALT normalization	If ALT levels were elevated (>ULN) at Baseline, ALT within normal limits on 2 consecutive visits or at the last visit*.
HBeAg loss (HBeAg-positive patients only)	Loss of detectable HBeAg if HBeAg was detected at Baseline.

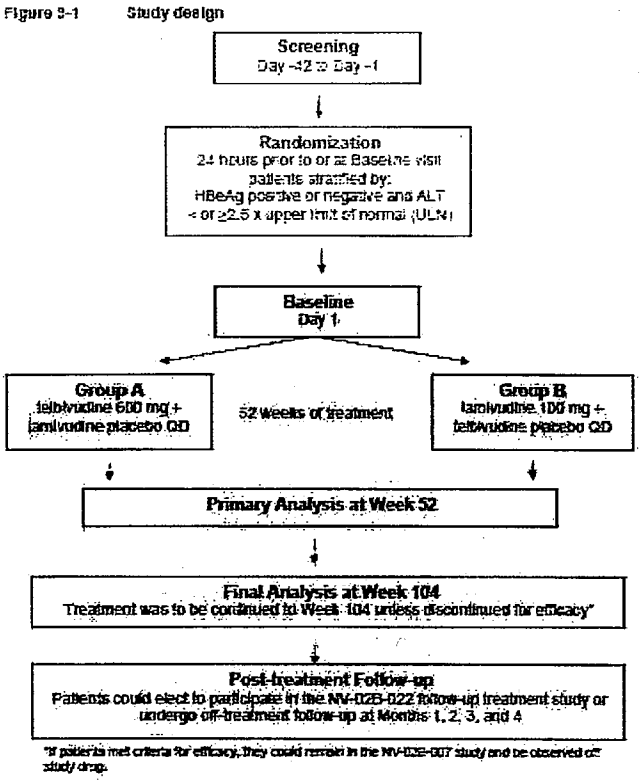
Endpoint	Definition
HBeAg seroconversion (HBeAg-positive patients only)	HBeAg loss and with gain of detectable HBeAb.
Virologic Response (HBeAg-positive patients only)	HBV DNA <5 log_{10} copies/mL and HBeAg loss.
3-Component HBeAg seroconversion (HBeAg-positive patients only)	HBeAg seroconversion and HBV DNA <5 log_{10} copies/mL.
HBsAg loss	Loss of detectable HBsAg if HBsAg was detected at Baseline.
HBsAg seroconversion	HBsAg loss and gain of detectable HBsAb.
Maintained endpoint response (for Therapeutic Response, HBV DNA, ALT normalization, HBeAg loss or seroconversion, or Virologic Response)	Response documented on at least 2 consecutive visits and at the last on-treatment evaluation with no 2 intervening consecutive disqualifying values.
Protocol-defined Virologic Breakthrough[†]	In patients with HBV DNA levels of ≥6 log_{10} copies/mL at Baseline, and who subsequently achieved 2 consecutive HBV DNA values <5 log_{10} copies/mL, Virologic Breakthrough is defined as HBV DNA ≥5 log_{10} copies/mL on 2 consecutive visits with no more than one subsequent value <5 log_{10} copies/mL, and with HBV DNA ≥5 log_{10} copies/mL at last treatment visit. If such a patient has a single HBV DNA value ≥5 log_{10} copies/mL at the last treatment visit, this result also qualifies as a Virologic Breakthrough. OR In patients with HBV DNA ≥6 log_{10} copies/mL at Baseline who never achieved 2 consecutive HBV DNA levels <5 log_{10} copies/mL but achieved ≥2 log_{10} copies/mL reduction from Baseline, Virologic Breakthrough is defined as a return of HBV DNA to within 1 log_{10} copies/mL of Baseline on 2 consecutive visits, with no more than one subsequent level >1 log_{10} copies/mL below Baseline through the last treatment visit. If such a patient has a single HBV DNA level within 1 log_{10} copies/mL of Baseline at the last treatment visit, this result also qualifies as a Virologic Breakthrough.
"1 log above nadir" Virologic Breakthrough	A confirmed HBV DNA increase of ≥1 log_{10} copies/mL above nadir HBV DNA (the lowest post-Baseline HBV DNA level achieved) in patients with a confirmed treatment response (2 consecutive ≥1 log_{10} copies/mL HBV DNA decreases below Baseline).
Treatment-emergent HBV resistance[#]	Protocol-defined or '1 log above nadir' Virologic

	breakthrough with genotypic evidence of resistance-associated mutations in HBV DNA amplified from patient sera.
Primary treatment failure	After completion of at least 24 weeks of treatment, HBV DNA never fell to <5 $\log_{10}$ copies/mL for 2 consecutive visits.
Secondary treatment failure	At Week ≥24, ALT increases to 10 × ULN on ≥2 visits over ≥7 days and either serum HBV DNA is ≥6 $\log_{10}$ copies/mL or the serum HBV DNA pattern meets the definition of protocol-defined Virologic Breakthrough, OR After Week 24, serum ALT level is ≥2 × ULN for 16 weeks and serum HBV DNA is either ≥6 $\log_{10}$ copies/mL or HBV DNA pattern meets the definition of protocol-defined 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 2 on-treatment visits, and (2) the last on-treatment serum HBV DNA value is ≥6 $\log_{10}$ copies/mL or the serum HBV DNA pattern meets either of the 2 definitions of protocol-defined Virologic Breakthrough.
Treatment discontinuation due to efficacy (qualifying criteria)	If HBeAg-positive at entry, completed ≥52 weeks of study drug treatment and exhibited HBeAg loss for ≥24 weeks, with HBV DNA < 5 log10 copies/mL at last visit, OR If HBeAg-negative at entry, completed ≥52 weeks of study drug treatment AND had HBsAg loss documented on ≥2 consecutive study visits.

*The last visit is defined as the last visit occurring prior to or on the date of the patient's data censoring.
†Section 2.2.2 of the NV-02B-015 SAP (Appendix 16.1.9).
#For this final Week 104 study report, data on treatment-emergent HBV resistance is omitted, pending a separate, detailed viral resistance report.

Study Design: Randomized, double-blind, multicenter phase 3 clinical trial to evaluate efficacy and safety of telbivudine (600 mg/day) vs. lamivudine (100 mg/day) in Chinese adults with chronic hepatitis B. The study design is shown in the following figure.

Figure 9. Study Design 015



Medical Officer Comments: *The study design for study 015 was virtually identical to that of study 007. This was a non-inferiority study, with a pre-specified non-inferiority margin of -15%. The primary analysis was performed at Week 52.*

Inclusion and Exclusion Criteria

The major inclusion and exclusion criteria for this study were similar to those in the 007 study. Male or female patients, ages 16 to 70 with documented chronic hepatitis B (as defined by all of the following: HBsAg-positive, liver biopsy within 12 months prior to randomization, and clinical history consistent with chronic hepatitis B) could be included in the study. Additionally, serum ALT was to be elevated at screening ($\geq$ 1.3- 10 x ULN), and HBV DNA $\geq$ 6 log10 copies/mL at screening. Patients were to be excluded for pregnancy or breastfeeding, co-infection with HIV, HCV, HCV or HDV, receipt of interferon for treatment of HBV in the previous 12 months, and history or clinical signs/symptoms of hepatic decompensation or hepatocellular carcinoma.

Study Procedures

The schedule of evaluations from screening through weeks 52 and 104 are shown in the following tables.

Table 56. Schedule of Evaluations (Baseline to Week 52)

Table 9-2 Evaluation and visit schedule through Week 52

	Screen	BL	Treatment week									
Evaluation/Event			2	4	8	12	16	24	32	40	48	52
Informed consent	X											
Medical history	X											
Eligibility review	X	X										
Vital signs (HR, BP)	X	X				X		X				X
Physical examination*	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X					X		X				X
Height	X											
HIV, HCV, HDV screens	X											
AFP	X											
Pregnancy test†	X	X		X	X	X	X	X	X	X	X	X
Prior/Concurrent medication review	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Blood samples for safety assessment and ALT	X	X	X	X	X	X	X	X	X	X	X	X
Prothrombin time	X	X										X
Urinalysis	X	X						X				X
HBV serologies	X	X				X		X	X	X	X	X
HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X
Liver biopsy	X§											X
Stored serum (for HBV genotype or repeat analyte testing)	X	X	X	X	X	X	X	X	X	X	X	X
Study drug adherence			X	X	X	X	X	X	X	X	X	X

BL = Baseline; HR = heart rate; BP = blood pressure
*Complete exam at Screening and Week 52; symptom-directed exam at other times.
†In women of child-bearing potential. Serum test at Screen and urine test at Week 52 required; urine test as indicated at other times.
§Within 12 months of entry and with 5 unstained slides available.

Medical Officer Comments: *In contrast to what is shown in the table above for liver biopsy, as described in the 015 study protocol, liver biopsies for assessment of histological response were not required in this Chinese study.*

Table 57. Schedule of Evaluations (Week 60 to 104)

Table 9-3 Evaluation and visit schedule Weeks 60 through 104

	Treatment week						
Evaluation/Event	60	68	76	84	92	100	104 or Early D/C
Vital signs (HR, BP)			X				X
Physical examination*	X	X	X	X	X	X	X
Body weight			X				X
Pregnancy test†	X	X	X	X	X	X	X
Concurrent medication	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Blood samples for safety assessment and ALT	X	X	X	X	X	X	X
Prothrombin time							X
Urinalysis							X
HBV serologies	X	X	X	X	X	X	X
HBV DNA	X	X	X	X	X	X	X
Stored serum (for HBV resistance or repeat analyte testing)	X	X	X	X	X	X	X
Study drug adherence	X	X	X	X	X	X	X

Early D/C = early discontinuation.
*Complete exam at Week 104 or Early D/C; symptom-directed exam at other times.
†In women of child-bearing potential. Urine test required at Week 104 or early termination, otherwise as indicated.

Patients who completed 104 weeks of treatment could be enrolled in the follow-up study, 022 which evaluated long term telbivudine treatment. Patients who did not enroll in that study, including those that discontinued treatment prematurely were to be followed monthly for 4 months. The follow-up schedule is shown in the following table. Patients who discontinued treatment for efficacy were to be followed on the regular 104 week visit schedule.

Table 58. Schedule of Evaluations (Post-Treatment)

Table 9-4 Evaluation and visit schedule for post-treatment follow-up

	Post Treatment			
Evaluation/Event	Month 1	Month 2	Month 3	Month 4
Vital signs (HR, BP)	X	X	X	X
Physical examination*	X	X	X	X
Pregnancy test (urine)†				X
Concurrent medication review	X	X	X	X
Adverse events	X	X	X	X
Blood samples for safety assessment and ALT	X	X	X	X
HBV serologies	X	X	X	X
HBV DNA	X	X	X	X
Stored serum (for HBV resistance or repeat analyte testing)	X	X	X	X

Note: Follow-up after treatment discontinuation at any time or if patient elects not to enter the follow-up study at Week 104.
*Complete exam at Month 4; symptom-directed exam at other times.
†In women of child-bearing potential at anticipated last follow-up visit

Samples for Serum HBV DNA were analyzed at the central reference laboratories using the COBAS Amplicor HBV Monitor PCR assay (lower limit of quantification estimated as ≤ 300 copies/mL). Serologic measurements and ALT analyses were performed at [redacted] Safety assessments included adverse events, laboratory assessments (hematology, chemistry and urinalysis), and assessment of vital signs, physical examination, and body weight. b(4)

Treatments: Patients were randomly assigned to telbivudine 600 mg plus lamivudine placebo daily for up to 104 weeks or to lamivudine 100 mg plus telbivudine placebo daily for up to 104 weeks. Patients were stratified by HBeAg status (positive or negative) and serum ALT level (< 2.5 x ULN vs. ≥ 2.5 x ULN). The interactive voice response system was used to randomly assign patients 1:1 to treatment groups.

Study Sites: 18 study centers in China

Study Populations

Primary: The Intent-to-Treat Population (ITT) was the primary analysis population. ITT was defined as all randomized patients who received at least one dose of study drug and had at least one observation after baseline.

Safety Population: ITT population

Efficacy Evaluable (EE) Population: All patients who presumptively received at least one dose of study medication, and who did not exhibit any major protocol criteria with regard to key entry

criteria. Note that according to the applicant, there were no major protocol violations in this study, and thus the EE population was identical to the ITT population.

Medical Officer Comments: *None of the clinical study sites were inspected by DSI for this study, so the statement that there were no major protocol violations in this study is difficult to evaluate.*

HBeAg Subpopulations
Some analyses were performed on both the HBeAg-positive or HBeAg-negative populations; and some endpoints were specific for certain HBeAg subpopulations (e.g. HBeAg seroconversion was definable only for HBeAg-positive subpopulation). The term, "Overall" population was used to include both HBeAg-positive and HBeAg-negative subpopulations. For the ITT analyses, the HBeAg subpopulation was determined based on IVRS system; while for the safety analyses, the HBeAg laboratory result obtained upon screening was used to define the subpopulations.

Patient Disposition
A total of 332 patients were randomized into the study, 165 to lamivudine, and 167 to telbivudine treatment. Patient disposition to week 52 and week 104 is summarized in the following table. Note that the ITT and EE populations are identical in this study. In the first year of the study, 5/165 (3%) lamivudine patients and 4/167 (2.4%) telbivudine patients were discontinued from the study for any reason; while in the second year 21/167 (12.7%) lamivudine and 11/167 (6.6%) telbivudine patients were discontinued. The most common reason for study discontinuation during both time periods was request (by patient, sponsor, or investigator). In the first year, 1 patient in each treatment group discontinued due to an adverse events; while in the second year of the study, 3/165 (1.8%) lamivudine and 2/167 (1.2%) telbivudine patients discontinued due to adverse events. There were no discontinuations for clinical disease progression or lack of efficacy in the first year, but in the second year, 4/165 (2.4%) lamivudine and no telbivudine patients discontinued for these reasons. One death was reported in the lamivudine group, and 2 in the telbivudine group. Deaths are further discussed below.

Table 59. Patient Disposition

Table 10-1 Patient disposition to Week 52 and to Week 104 – all populations

	Lamivudine		Telbivudine		Total	
Patient populations	N	(%)	N	(%)	N	(%)
Randomized patients	165	100	167	100	332	100
ITT & Safety populations	165	100	167	100	332	100
EE population	165	100	167	100	332	100
Patients discontinued from study to Week 52	n	(%)	n	(%)	n	(%)
ITT, Safety, EE populations - any reason	5	(3.0)	4	(2.4)	9	(2.7)
Noncompliance	0		0		0	
Pregnancy	0		0		0	
Adverse event	1	(0.6)	1	(0.6)	2	(0.6)
Clinical disease progression	0		0		0	
Lack of efficacy after Week 24	0		0		0	
Death	0		1	(0.6)	1	(0.3)
Request*	4	(2.4)	2	(1.2)	6	(1.8)
Patients discontinued from study to Week 104						
ITT, Safety, EE populations - any reason	21	(12.7)	11	(6.6)	32	(9.6)
Noncompliance	2	(1.2)	2	(1.2)	4	(1.2)
Pregnancy	1	(0.6)	1	(0.6)	2	(0.6)
Adverse event(s)	3	(1.8)	2	(1.2)	5	(1.5)
Clinical disease progression	2	(1.2)	0		2	(0.6)
Lack of efficacy after Week 24	2	(1.2)	0		2	(0.6)
Death	1	(0.6)	1	(0.6)	2	(0.6)
Request*	10	(6.1)	5	(3.0)	15	(4.5)

* Patient, Investigator or Sponsor-initiated request

Medical Officer Comments: *Discontinuations were infrequent in both treatment groups in this study.*

Criteria for Discontinuation Due to Efficacy

HBeAg-positive patients (at entry) could discontinue treatment after completion of 52 weeks of study drug if HBV DNA level was < 5 log10 copies/mL with HBeAg loss for at least 24 weeks. HBeAg-negative patients (at entry) could discontinue treatment if HBsAg loss at week 52 or thereafter was confirmed on two consecutive visits. Patients who discontinued treatment for efficacy were to remain on study complete the scheduled study visits. Patients who relapsed were to remain blinded and restart their originally assigned regimen.

Demographics

The treatment groups were similar with respect to age, gender. All patients were Chinese. Most study participants were male (78.6% overall), ranging in age from 15 to 64 years old, with a median age of 28 years old.

Underlying Disease and Treatment

Most patients were diagnosed with hepatitis B more than a year prior to study entry, although a higher proportion of patients in the telbivudine treatment arm (97%) were diagnosed ≥ 1 year prior, in comparison to 89% in the lamivudine arm, in which a higher proportion of patients (9%) were diagnosed > 6 months < 1 year prior to entry than in the telbivudine arm (2.4%). Similarly,

3/165 (1.8%) of patients in the lamivudine group were diagnosed within 6 months prior to study entry compared to 1/167 (0.6%) in the telbivudine group. Median duration of HBV infection was 4 years (range 0.3 to 30 years) in the lamivudine group and 6 years (range 0.3 to 28 years) in the telbivudine group.

Overall 9% of study participants had received prior alpha-interferon therapy, 12.6% in the telbivudine treatment arm, and 5.5% in the lamivudine treatment arm. Patients could not have received interferon treatment within 12 months prior to study entry. The majority of patients in both treatment groups who had received prior interferon therapy had been considered treatment failures (due to lack of efficacy) on interferon.

Baseline HBV Serology
All study participants were HBsAg as per the inclusion criteria. Similar proportions of patients were HBeAg-positive (approximately 85%) or HBeAg-negative (approximately 15%) in the two treatment groups; and similar proportions were HBeAb-positive (22%) or HBeAb-negative (78%). Mean and median baseline HBV DNA levels were also similar in the telbivudine and lamivudine groups, with a mean level of 9.16 and 9.39 copies/$\log_{10}$ copies/mL, respectively.

Baseline HBV Genotypes
The majority of patients in each of the treatment groups were HBV genotype C, 101/167 (60.5%) in telbivudine group, and 109/165 (66.1%) in the lamivudine group. The remainder of patients were HBV genotype B, 64/167 (38.3%) in the telbivudine group, and 56/165 (33.9%) in the lamivudine group, and two had unknown HBV genotype in the telbivudine group.

Medical Officer Comments: *HBV genotypes B and C are the most common genotypes found in Asia; however, in the U.S., the most common HBV genotype is A, and as HBV genotype may affect treatment response, the generalizability of the results of this study to the U.S. population could be an issue.*

Baseline Liver Function Tests
In the ITT population, there was no statistically significant difference in mean or median ALT, albumin or total bilirubin values, although the median ALT was numerically higher in the telbivudine treatment group (119 IU/L compared to 105 IU/L for lamivudine). Most patients in both groups had baseline ALT values between 2 and 5 x ULN (42 or 43% in both treatment arms), with a mean ALT multiple of the ULN of 3.55 in the lamivudine group and 3.46 in the telbivudine group.

Baseline Liver Histology
Baseline histology was available in 144/165 (87%) patients in the lamivudine group, and in 152/167 (91%) patients in the telbivudine group. Similar proportions of patients in each group had a baseline Knodell Histology Activity Index (HAI) score of ≤ 10 (74% lamivudine; 72% telbivudine) or > 10 (26% lamivudine; 28% telbivudine). The Knodell HAI score has a range of 0-18 based on a sum of the periportal and bridging necrosis score (0-10), intralobular degeneration and focal necrosis score (0-4) and the portal inflammation score (0-4). The Knodell fibrosis score is scored from 0-4; while the Ishak fibrosis score measures fibrosis on a scale of 0 (no fibrosis) to 6 (established cirrhosis). Ishak scores of 1 and 2 indicate degrees of portal

fibrosis, 3 and 4 indicate bridging fibrosis, and 5 indicates nodular or incomplete cirrhosis. Baseline histology parameters for study participants are shown in the following table.

Table 60. Mean Baseline Histology Parameters in the ITT-Histology Evaluable Population (from applicant's Table 11-7, 015 Study Report)

Histology Parameter	Lamivudine N=144	Telbivudine N=152
Mean Knodell HAI Score (SE) (0-18)	7.83 (0.304)	8.21 (0.301)
Mean Knodell Fibrosis Score (SE) (0-4)	1.49 (0.086)	1.72 (0.087)
Mean Ishak Fibrosis Score (SE) (0-6)	1.98 (0.098)	2.15 (0.091)

SE = standard error

Medical Officer Comments: *Mean baseline values for the Knodell HAI score and both fibrosis scores were generally similar between treatment groups.*

Efficacy Outcomes

Primary Endpoint: HBV DNA Reduction

Serum HBV reduction was defined as reduction in serum HBV DNA (in $\log_{10}$ copies/mL) from baseline values at the post-baseline study visits. Primary treatment comparison was at week 52; with a secondary comparison at week 104.

The following table shows HBV DNA reduction from baseline at weeks 24, 52, 76, and 104 in the overall ITT population, and in the HBeAg-positive and negative subpopulations. In the overall ITT population, at week 52 mean HBV DNA was reduced -6.22 $\log_{10}$ copies/mL in the telbivudine treatment group, and -5.40 $\log_{10}$ in the lamivudine treatment group. The p-value for the treatment difference was 0.0004. At week 104 in the overall ITT population, HBV DNA was reduced -5.48 $\log_{10}$ copies/mL in the telbivudine group and - 4.00 $\log_{10}$ copies/mL in the lamivudine group. The p-value for the treatment difference was < 0.0001.

For the HBeAg-positive subpopulation, mean HBV DNA reduction in the telbivudine and lamivudine treatment arms were -6.33 and -5.49 $\log_{10}$ copies/mL, respectively (p=0.0008) at 52 weeks and -5.47 and -3.97 $\log_{10}$ copies/mL, respectively (p= 0.0001) at 104 weeks. In the HBeAg-negative subpopulation, there was no significant difference between the treatment groups at 52 or 104 weeks.

Table 61. HBV DNA Reduction from Baseline

Table 11-9 HBV DNA reduction (log_{10} copies/mL) from Baseline at Weeks 24, 52, 76 and 104 - ITT population

	HBeAg positive		HBeAg negative		Overall	
Time point	Lamivudine (N=143)	Telbivudine (N=147)	Lamivudine (N=22)	Telbivudine (N=20)	Lamivudine (N=165)	Telbivudine (N=167)
Week 24						
Mean (SE)	-5.54 (0.15)	-6.35 (0.15)	-4.72 (0.36)	-5.49 (0.38)	-5.43 (0.14)	-6.24 (0.14)
P-value		0.0001		0.1536		< 0.0001
Week 52						
Mean (SE)	-5.49 (0.18)	-6.33 (0.18)	-4.81 (0.38)	-5.49 (0.40)	-5.40 (0.16)	-6.22 (0.16)
P-value		0.0008		0.2323		0.0004
Week 76						
Mean (SE)	-4.25 (0.25)	-5.76 (0.25)	-4.66 (0.41)	-5.57 (0.42)	-4.31 (0.23)	-5.74 (0.22)
P-value		< 0.0001		0.1314		< 0.0001
Week 104						
Mean (SE)	-3.97 (0.27)	-5.47 (0.26)	-4.20 (0.49)	-5.59 (0.51)	-4.00 (0.24)	-5.48 (0.24)
P-value		0.0001		0.0558		< 0.0001

p-value for treatment group differences by ANOVA controlling for randomization strata
Source: Table 14.2.1.1, Table 14.2.1.3, Table 14.2.1.5

Medical Officer Comments: *Based on this analysis, for the primary endpoint in this study, HBV DNA reduction in the telbivudine group was significantly greater than in the lamivudine group at week 52, at week 104 in the overall population and HBeAg-positive population, but not for the HBeAg-negative population. However, the numbers of HBeAg-negative patients were small.*

Secondary Endpoints: A number of secondary endpoints were evaluated in this study. The key secondary endpoint was Therapeutic Response at week 52 (serum HBV DNA < 5 log_{10} copies/mL and either HBeAg loss or ALT normalization). Note that histologic response was not measured as an outcome in this study.

Medical Officer Comments*: Note that this study was not sufficiently powered to test Therapeutic Response for the treatment difference between lamivudine and telbivudine.*

Key Secondary Endpoint: Therapeutic Response
Therapeutic Response is a composite endpoint requiring suppression of HBV DNA to levels below 5 log_{10} copies/mL plus either clearance of HBeAg or ALT normalization. The following table shows Therapeutic Response by treatment and HBeAg status. Based on a non-inferiority margin of -15%, in the overall population, telbivudine was superior to lamivudine for therapeutic response at weeks 52 and 104. For the HBeAg-positive subpopulation, telbivudine was superior to lamivudine at 52 and 104 weeks; while in the HBeAg-negative subpopulation, superiority of telbivudine over lamivudine was demonstrated only at week 52, but not week 104.

Table 62. Therapeutic Response

Table 11-11 Patients with Therapeutic Response at Week 52 and Week 104 by treatment and HBeAg status - ITT population

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	CI [1]	P-value [2]
Week 52				
Overall	106/165 (64.1)	145/167 (86.9)	(8.0, 37.6)	< 0.0001
HBeAg-positive	88/143 (61.5)	125/147 (85.0)	(13.4, 33.6)	< 0.0001
HBeAg-negative	18/22 (81.8)	20/20 (100)	(1.6, 34.8)	0.0270
Week 104				
Overall	73/165 (44.0)	115/167 (69.0)	(8.2, 41.8)	< 0.0001
HBeAg-positive	58/143 (40.5)	97/147 (66.0)	(14.2, 36.7)	< 0.0001
HBeAg-negative	15/22 (68.2)	18/20 (90.0)	(-2.0, 45.7)	0.0645

[1] 99.9067% 2-sided CI for the difference in the therapeutic response rate between the treatment groups
[2] p-value for treatment group differences controlling for randomization strata; difference between proportions for categorical variables
Note: Percentages, confidence intervals and p-values were calculated using Mantel-Haenszel weighted estimates based on randomization strata:
Source: Table 14.2.1.1, Table 14.2.1.3, Table 14.2.1.5

Medical Officer Comments: *For the Therapeutic Response Endpoint in study 015 telbivudine was non-inferior and superior to lamivudine in both HBeAg subpopulations at Week 52. At week 104, in this study, telbivudine was non-inferior to lamivudine in both HBeAg subpopulations, and was superior to lamivudine in the HBeAg-positive group.*

Therapeutic Response was also evaluated in the ITT population by randomization strata (i.e. by HBeAg status and ALT < 2.5 or ≥ 2.5 x ULN). Telbivudine was found to be superior to lamivudine at weeks 52 and 104 in the HBeAg-positive/ ALT < 2.5 x ULN and HBeAg-positive/ ALT ≥ 2.5 x ULN strata; but in the HBeAg-negative strata, telbivudine was non-inferior, but was not superior to lamivudine except in the HBeAg-negative/ALT ≥ 2.5 x ULN strata at 104 weeks.

Other important secondary endpoints in this study are summarized in the following table.

Table 63. Virologic, Biochemical, and Serologic Endpoints at Weeks 52 and 104 in Study NV-02B-015 in ITT population

Response Parameter	HBeAg-positive N=921		HBeAg-negative N=446	
	Telbivudine N=147	Lamivudine N=143	Telbivudine N=20	Lamivudine N=22
Week 52				
% Subjects HBV DNA negative by PCR	67% N=147	38% N=143	85% N=20	77% N=22
ALT normalization	87% N=142	75% N=135	100% N=18	78% N=18
HBeAg seroconversion	25% N=138	18% N=138)	NA	NA
HBeAg Loss	31% N=138	20% N=138	NA	NA
Week 104				
% Subjects HBV DNA negative by PCR	58% N=147	34% N=143	90% N=20	68% N=22
ALT normalization	73% N=142	59% N=135	95% N=18	78% N=18
HBeAg seroconversion	29% N=138	20% N=138	NA	NA
HBeAg Loss	40% N=138	28% N=138	NA	NA

Source: NV-02B-015 Study Report

Medical Officer Comments: Among HBeAg-positive patients, at weeks 52 and 104, a higher proportion of patients treated with telbivudine had undetectable HBV DNA by PCR, ALT normalization, HBeAg loss or HBeAg seroconversion. Similarly, for HBeAg-negative patients, a higher proportion had undetectable HBV DNA and ALT normalization in the telbivudine than the lamivudine group.

Discontinuations Due to Efficacy

A total of 4 patients in the lamivudine group and 1 in the telbivudine group discontinued treatment early due to efficacy. No further analysis of these patients was performed for this review because of the small numbers of patients met discontinuation criteria and discontinued therapy.

Virologic Breakthrough
The "1 log greater than nadir breakthrough", an HBV elevation of at least 1 $\log_{10}$ copies/mL above HBV DNA nadir after initial drop of $\geq$ 1 $\log_{10}$ copies/mL from baseline was determined for weeks 48 and 104. At both time points, the proportion of patients with virologic breakthrough was higher in the lamivudine than the telbivudine group as shown in the following table.

Table 64. Virologic Breakthrough* at Week 48 and 104

Treatment Group	Week 48 n/N (%)	Week 104 n/N (%)
Lamivudine	26/165 (15.8)	85/165 (51.7)
Telbivudine	11/167 (6.5)	43/167 (25.6)

*1 log greater than nadir breakthrough
Source:

Medical Officer Comments: *In both treatment groups, the proportion of patients with virologic breakthrough increased from week 48 to 104 on-treatment. Although breakthrough was higher in the lamivudine group for both time points, a fairly high proportion (26%) of patients on telbivudine also had breakthrough through 2 years on the study.*

Discussion of Efficacy Findings in Study 015
Study NV-02B-015 can be considered supportive for the efficacy findings in the pivotal study, NV-02B-007. This was a randomized, controlled, double-blinded 104 week study of telbivudine vs. lamivudine conducted in China for registrational purposes. The primary endpoint for this study was mean HBV DNA reduction. Additionally, although histology was required for study entry, histologic response was not measured as an outcome.

For the primary endpoint, mean HBV reduction was greater in telbivudine than lamivudine treated patients at weeks 52 and 104 in the overall population and the HBeAg-positive subpopulation. For the important secondary endpoints, proportion of patients with undetectable HBV DNA, ALT normalization, HBeAg loss and seroconversion, a favorable response was reported in higher proportion of telbivudine than lamivudine recipients at Week 52 and 104. Additionally a higher proportion of lamivudine- than telbivudine-treated patients experienced virologic breakthrough at weeks 48 and 104.

Safety Outcomes in Study NV-02B-015
The safety population consisted of all patients who received at least one dose of study medication with at least one observation after baseline (ITT population). Three treatment periods were defined for analysis of safety:

On Treatment: from baseline to date of last treatment plus 7 days; and from re-starting blinded medication to 7 days post last treatment.

Off treatment: from 8 days after last treatment, date of study discontinuation, or date of restarting therapy, whichever was applicable through follow-up period. Patients who discontinued therapy due to efficacy were included in the off-treatment analyses.

Post-treatment: from 8 days after last treatment through end of follow-up period (4 months) for those who discontinued treatment prematurely or those who elected not to enter the rollover study, -022.

Study Drug Exposure: Patients received either 600 mg telbivudine or 100 mg lamivudine daily for up to 104 weeks. Dose modifications were not permitted. Median exposure was 104 weeks in both treatment groups; while mean exposure was slightly higher in the telbivudine group (101.6 vs. 99.9 weeks), as shown in the following table. Note that 69-75% of patients had exposures ≥ 104 weeks; while 25-21% had between 76 and 104 weeks in the lamivudine and telbivudine groups, respectively.

Table 65. Overall Treatment Exposure

Table 12-1 Overall treatment exposure (weeks) - ITT population

Exposure (weeks)	Lamivudine (N=165)	Telbivudine (N=167)	Total (N=332)
< 24 weeks	1 (0.6)	1 (0.6)	2 (0.6)
>= 24 - <52 weeks	1 (0.6)	1 (0.6)	2 (0.6)
>= 52 - <76 weeks	9 (5.5)	5 (3.0)	14 (4.2)
>= 76 - <104 weeks	41 (24.8)	35 (21.0)	76 (22.9)
>= 104 weeks	113 (68.5)	125 (74.9)	238 (71.7)
Mean (SE)	99.91 (0.997)	101.55 (0.889)	100.74 (0.668)
Median	104.00	104.00	104.00
25%, 75%	103.86, 104.14	103.86, 104.29	103.86, 104.29
Range	18.9, 106.3	18.1, 106.0	18.1, 106.3

Note: Duration of study treatment therapy is number of weeks from the baseline date to the last visit date on study for ongoing patients, the last dose date for patients who completed or discontinued the study early, or the day before treatment discontinuation for patients who discontinued due to efficacy

Summary of Adverse Events in Study 015

The proportion of patients with any adverse event was slightly higher in the telbivudine than in the lamivudine treatment arm, as summarized in the following table. Additionally, those adverse events considered at least possibly drug-related by the investigator were somewhat more common in the telbivudine group; while moderate-severe adverse events and discontinuations due to adverse events were somewhat more frequent in the lamivudine group. In both treatment groups, the proportion of patients with adverse events was higher from baseline to Week 52 than from week 52 to End-of-Study (Week 104) (e.g. 95/167, 56.9% telbivudine-treated patients experienced an adverse event in the first year, compared to 62/167, 37.1% patients in the second year of the study).

Table 66. Summary of Adverse Events (on-treatment) in Study 015 from Baseline to End-of-Study

Parameter	Lamivudine N=165 n/N (%)	Telbivudine N=167 n/N (%)
Patients with any adverse event	100 (60.6)	108 (64.7)
Patients with any drug-related adverse event	11 (6.7)	21 (12.6)
Patients with Moderate-Severe adverse event	42 (25.5)	36 (21.6)
Patients with Serious Adverse Event	11 (6.7)	6 (3.6)
Deaths	1 (0.6)	1 (0.6)
Patients who discontinued treatment due to adverse event	7 (4.2)	5 (2.9)
Patients who discontinued treatment due to SAE	3 (1.8)	2. (1.2)

***Medical Officer Comments**: Note that the proportion of patients with any adverse event in this study is lower than that observed in Study 007 (77% lamivudine patients and 81% telbivudine patients in that study had at least one adverse event). Adverse events considered drug-related by the investigator were also less frequent in this study (e.g. for telbivudine 29% patients in the 007 Study compared to 13% in Study 015). Whether this is due to differences in reporting AEs (by patients or investigators) or to differences in population (e.g. racial differences) between the studies is not known. The proportion of patients with serious adverse events or who discontinued due to adverse events was similar in both studies.*

Deaths

Two deaths were reported in this study. Patient 008-022 who was treated with lamivudine experienced an exacerbation of hepatitis B (on-treatment) which resulted in death; and patient 010-001, who was treated with telbivudine was murdered while on-treatment.

***Medical Officer Comments:** Narrative summaries for these two deaths were reviewed. There was no obvious relationship between the murder and study medication (telbivudine) in Patient number 010-001. For the lamivudine patient who died due to exacerbation of hepatitis B, assessment of potential relationship to study medication is not as straightforward. In that case, the patient, a 26 year old Chinese male with HBeAg-positive chronic hepatitis B and compensated liver disease presented on Study Day 470 with a 10-day history of malaise, nausea, and anorexia. ALT and AST levels were found to be markedly elevated (1482 and 722 IU/L, respectively) and total bilirubin was elevated at 2.99 mg/dL. The patient was hospitalized, found to be negative for HAV, HCV, but was positive for HEV (IgG-positive). He continued on lamivudine, but was also treated with dexamethasone, hepatocyte growth-promoting factor, and*

a number of other medications. He continued to deteriorate, and was started on adefovir on Day 488. This patient had a baseline HBV DNA of 12.8 log10 copies/mL. The patient died due to hepatic failure on Day 493. On review of the efficacy dataset, RSP, this patient experienced ALT normalization and HBV DNA < 5 log10 copies/mL (successful Therapeutic response) by study Day 169- 365; he subsequently had virologic breakthrough (Day 421), with HBV DNA continuing to rise through Day 489 (to a max of 12.52 log10 copies/mL). Although not likely directly related to study drug (lamivudine), this patient experienced a severe acute exacerbation of hepatitis B with virologic breakthrough and treatment failure, not improved with addition of adefovir, with subsequent hepatic failure and death. Hepatitis E virus, which is foodborne, could potentially have contributed to the exacerbation of hepatitis; however that seems unlikely because HEV IgG was detected, most likely indicating prior rather than current infection. HEV IgM was not reported. Whether treatment with dexamethasone further exacerbated hepatitis B is not known.

Serious Adverse Events

Serious adverse events on-treatment were reported in 11/165 (6.7%) lamivudine- and 6/167 (3.6%) telbivudine-treated patients from baseline to end-of-study. Additionally, one serious adverse event was reported post-treatment in a patient treated with lamivudine (increased ALT). In the lamivudine group, more patients reported SAEs in the second year of the study in comparison to the first year; while the opposite was true for patients treated with telbivudine. The most common SAE in both treatment groups was exacerbation of hepatitis B (reported as hepatitis B). Serious adverse events are shown in the following table by onset.

Table 67. Serious Adverse Events in Study 015

Adverse Event (Preferred Term)	Baseline to Week 52	Baseline to Week 52	Week 52 to End of Study (Week 104)	Week 52 to End of Study (Week 104)	Baseline to End-of-Study (Week 104)	Baseline to End-of-Study (Week 104)
Treatment Group	Lamivudine N=165	Telbivudine N=167	Lamivudine N=165	Telbivudine N=167	Lamivudine N=165	Telbivudine N=167
Patients with SAE [n/N (%)]	3 (1.8)	4 (2.4)	8 (4.8)	2 (1.2)	11 (6.7)	6 (3.6)
Hepatitis B	2	2	6	2	8	4
Head injury	1	0	0	0	1	0
Polymyositis	0	1	0	0	0	1
Murder	0	1	0	0	0	1
Lymphadenitis	0	0	1	0	1	0
Hepatic failure	0	0	1	0	1	0

Source: A_AE dataset for 015

Medical Officer Comments: *Note that the two deaths in this study were also included with serious adverse events, one in each treatment group (hepatitis B-lamivudine, and murder-*

telbivudine). Additionally, more patients had exacerbations of hepatitis B in the lamivudine than the telbivudine treatment group.

Table 68. Non-Fatal SAEs reported on-treatment with telbivudine

Patient ID	Event Preferred Term	Date Onset	Study Day Onset	Relationship to Study Drug (applicant's assessment)	Outcome
Telbivudine					
CHN/0008/00013	Acute exacerbation Hepatitis B		Day 706	Not related	Recovered
CHN/0008/00018	Acute exacerbation hepatitis B	16 Jan 2006	Day 535	Not related	LdT Discontinued
CHN/0008/00021	Acute exacerbation hepatitis B	26 November 2004	Day 121	Not related	Recovered
CHN/00010/00023	Polymyositis	8 July 2005	Day 325	Not related	Recovered
CHN 0017/00007	Acute exacerbation hepatitis B	15 July 2005	Day 337	Not related	Recovered
Lamivudine					
CHN/0006/00005	Lymphadenitis (Grade 3)	9 November 5005	Day 456	Not related	Ongoing
CHN/0007/00024	Hepatitis B (Grade 3)	14 November 2005	Day 435	Not related	Study med discontinued; improved; cirrhosis and splenomegaly shown on ultrasound
CHN/008/00008	Acute exacerbation hepatitis B	20 April 2005	Day 265	Not related	Recovered; study medication stopped Day 420 (unknown reason)
CHN/008/00026	Acute exacerbation hepatitis B	14 November 2005	Day 474	Not related	Recovered

	(Grade 3)				
CHN/0009/00035	Hepatic failure	2 February 2006	Day 534	Not related	Entecavir started ; Study medication stopped Day 637; recovered
CHN/0011/00016	Hepatitis B flare (grade 3)	27 August 2004	Day 2	Not related	Recovered
CHN/0012/00003	Acute exacerbation hepatitis B (grade 4)	23 November 2005	Day 478	Not related	Study medication discontinued (resistance mutation detected); started adefovir and lamivudine; recovered
CHN/0012/00029	Acute exacerbation hepatitis B (grade 4)	14 March 2006	Day 589	Not related	Adefovir started; study medication stopped; recovered
CHN/0013/00011	Increased ALT (HBV flare, grade 3)	5 April 2006	Day 594	Related	Resistant HBV mutation detected; adefovir started; study medication discontinued; recovered
CHN/0019/00018	Head injury	30 May 2005	Day 286	Not related	Recovered; study medication temporarily interrupted

Medical Officer Comments: *The narrative summaries for the serious adverse events in this study were reviewed. Only one SAE in this study was considered related to study medication by the applicant and investigator. This was a hepatitis B flare during the second year of the study in a patient who received lamivudine (Patient* CHN/0013/00011*). A total of 8 lamivudine recipients experienced acute exacerbations of hepatitis B or hepatic failure. In the telbivudine treatment*

group, 4 patients experienced acute exacerbations of hepatitis B. For the cases of on-treatment hepatitis B exacerbation in either treatment group, in most cases, ALT increases were associated with increased HBV DNA levels. In many cases study medication was continued and the event resolved spontaneously or with treatment (e.g. herbal medications, glutathione, glycyrrhizic acid, and sometimes adefovir or entecavir). Acute exacerbations of hepatitis B while on treatment have also been reported with other anti-HBV agents, and are probably not due to drug toxicity.

Polymyositis was reported as an SAE in a patient who received telbivudine. This patient developed CK elevations starting approximately 2 months after starting medication, these persisted and the patient developed pain in the upper abdomen and chest, arms and legs, edema in both feet and difficulty in climbing stairs. An EMG performed Day 324 revealed a myopathic process and the patient was hospitalized. Physical examination revealed normal muscle strength, tone and reflexes in all four limbs. A muscle biopsy performed Day 380 showed partial muscle fibrosis, mild muscle atrophy, and "partial rhabdomyolysis" (re-translated by the applicant as muscle atrophy and lysis of muscle fibers, and an official retranslation is being obtained). Telbivudine was continued throughout. The patient was treated with corticosteroids and a number of vitamins, and improved. Given the known safety profile of telbivudine, the medical officer considers this SAE, polymyositis, to be probably related to telbivudine.

One post-treatment SAE was reported in this study, increased ALT (grade 3) in a lamivudine-treated patient (number CHN/0014/0005). Transaminase elevation was observed 4 months after receiving the last dose of study medication (lamivudine). At the same time, HBV DNA was 9.8 $\log_{10}$ copies/mL, and thus this event was likely due to relapse. The investigator considered this event not related to study medication.

Moderate to Severe Adverse Events

A total of 42/165 (25.5%) lamivudine- and 36/167 (21.6%) telbivudine-treated patients experienced at least one moderate to severe (Grade 2 to 4) adverse events during the two years of the study. Note that if a patient had more than 1 moderate to severe adverse event, he/she was counted only once. In the telbivudine group, a total of 31 patients experienced 48 adverse events of Grade 2 intensity; 5 patients experienced 6 adverse events of Grade 3 intensity, and 3 patients experienced 3 AEs of Grade 4 intensity. In the lamivudine group, 33 patients experienced 58 Grade 2 adverse events, 8 patients experienced 9 Grade 3 adverse events, and 4 patients experienced 4 Grade 4 adverse events. The most common moderate to severe adverse events are shown in the following table.

Table 69. Adverse Events of Moderate to Severe Intensity

Adverse Event (Preferred Term)	Lamivudine N=165	Telbivudine N=167
Number of patients with any Grade 2-4 AE	42 (25.5)	36 (21.6)
Nasopharyngitis	4 (2.4)	**8 (4.8)**
Fatigue	1 (0.6)	0
Toothache	1 (0.6)	2 (1.2)
Hepatitis B	**13 (7.9)**	6 (3.6)
CK increased	1 (0.6)	6 (3.6)
ALT increased	3 (1.8)**	3 (1.8)
Pyrexia	3 (1.8)	2 (1.2)
Gastric ulcer	0	**2 (1.2)**
Abdominal pain, upper	1 (0.6)	2 (1.2)
Tonsillitis	2 (1.2)	1 (0.6)
Upper respiratory infection	**3 (1.8)**	0
Gastritis	**3 (1.8)**	1 (0.6)
Reflux esophagitis	1 (0.6)	0
Perihepatic discomfort	1 (0.6)	0
Diarrhea	**2 (1.2)**	0
Lymphadenitis	1 (0.6)	0
Platelet count decreased	1 (0.6)	0
Hepatic failure	1 (0.6)	0
Polymyositis	0	1 (0.6)

Source: A/AE dataset for Study 015
** Two episodes of increased ALT occurred post-treatment

Medical Officer Comments: *More telbivudine-treated patients experienced Grade 2-4 nasopharyngitis, increased CK and gastric ulcer than lamivudine-treated patients. Conversely, lamivudine-treated patients experienced more Grade 2-4 hepatitis B (exacerbation), upper respiratory infection, gastritis and diarrhea than telbivudine recipients.*

Adverse Events Resulting in Treatment Interruption or Discontinuation
A total of 7/165 (4.2%) patients who received lamivudine and 5/167 (3.0%) patients who received telbivudine either discontinued or interrupted study drug due to an adverse event from baseline to End-of-Study. Adverse events resulting in treatment interruption in the lamivudine group included lymphadenitis (1 patient), tonsillitis (1patient), head injury and soft tissue injury (1 patient); and in the telbivudine group included fatigue and hepatic pain in 1 patient, and gastroenteritis in one patient. Four patients in the lamivudine group discontinued treatment due to adverse events, including hepatic failure (1), hepatitis B (2 patients), and vomiting (1); while 3 patients in the telbivudine group discontinued therapy due to pain in extremity (1), hepatitis B (1), and murder (1).

Significant Adverse Events

Musculoskeletal Adverse Events

The applicant analyzed adverse event terms possibly related to the myopathic/muscle injury process (asthenia, fatigue, malaise, muscular weakness, musculoskeletal discomfort, musculoskeletal pain, myalgia, myopathy, myositis, pain, pain in the extremity, and polymyositis) occurring within approximately 30 days of a new onset CK elevation from baseline to end-of-study.. No such events (associated with CK elevation) were reported among lamivudine-treated patients, while 4 telbivudine treated patients experienced such events associated with any CK elevation (grade 1-4) in the first 52 weeks of the study, and an additional 8 telbivudine-treated patients experienced such events associated with any CK elevation (grades 1-4) from week 52 to end-of study. These events are shown in the following table. Note that the percentage of patients shown for adverse events in the table below is in reference to the number of patients with a new-onset CK elevation grouped as Grade 1/2, 3/4, or 1/4. The number of patients in each CK category is shown in bold type.

Table 70. Summary of Musculoskeletal Adverse events associated with new-onset CK elevation in Safety Population

	Lamivudine N=165 n (%)	Telbivudine N=165 n (%)
Baseline to Week 52		
Within new onset Grade 1/2 CK elevation	**38**	**117**
Patients reporting Adverse Event	0	2 (1.7)
Asthenia	0	0
Fatigue	0	1 (0.9)
Muscular weakness	0	1 (0.9)
Myalgia	0	1 (0.9)
Pain in extremity	0	0
Within new onset Grade 3/4 CK elevation	**5**	**14**
Patients reporting Adverse Event	0	2 (14.3)
Asthenia	0	1 (7.1)
Fatigue	0	1 (7.1)
Muscular weakness	0	1 (7.1)
Myalgia	0	0
Pain in extremity	0	1 (7.1)
Within new onset Grade 1/4 CK elevation	**38**	**118**
Patients reporting Adverse Event	0	4 (3.4)
Asthenia	0	1 (0.8)
Fatigue	0	2 (1.7)
Muscular weakness	0	1 (0.8)
Myalgia	0	1 (0.8)
Pain in extremity	0	1 (0.8)
Week 52 to End of Study		
Within new onset Grade 1/2 CK elevation	**39**	**118**
Patients Reporting Adverse Event	0	8 (6.8)
Fatigue	0	6 (5.1)
Pain in extremity	0	1 (0.8)
Polymyositis	0	1 (0.8)
Within new onset Grade 3/4 CK elevation	**1**	**7**
Patients reporting adverse event	0	1 (14.3)
Fatigue	0	0
Pain in extremity	0	0
Polymyositis	0	1 (14.3)
Within new onset Grade 1/4 CK elevation	**39**	**119**
Patients reporting adverse event	0	8 (6.7)
Fatigue	0	1 (5.0)
Pain in extremity	0	
Polymyositis	0	1 (0.8)

Source: Tables 14.3.1.3.5.10 and 14.3.1.3.5.11 Study Report 015

CK Elevations: See section below on new-onset laboratory abnormalities.

Peripheral Neuropathy
No cases of peripheral neuropathy were reported in this study. Two telbivudine- and one lamivudine-treated patient experienced hypoaestheia of one or more extremities. No reports of paraesthesia, dysesthesia, sensory loss were identified in the A_AE dataset for this study.

ALT Flares
Using the AASLD definition of ALT (hepatitis) flares (ALT > 2 x baseline and > 10 X ULN), 16/165 (9.7%) lamivudine- and 13/167 (7.8%) telbivudine recipients experienced an ALT flare on-treatment. Post-treatment, 3/22 (13.6%) lamivudine patients and 0/23 telbivudine patients who discontinued prematurely for reasons other than efficacy, or completed the study and elected not to enroll in the follow-up study 022, experienced an ALT flare based on the AASLD definition.

Laboratory Abnormalities
New onset laboratory abnormalities were defined as laboratory assessments with increased toxicity grade compared with baseline values. The following table shows new-onset Grade 3 or 4 laboratory abnormalities from baseline to Week 52, and post week 52 to Week 104. The proportion of patients with Grade 3 or 4 CK elevation was higher in the telbivudine group for both treatment periods; while the proportion of patients with Grade 3 or 4 ALT or AST or bilirubin elevation was higher in the lamivudine treatment group. The numbers of patients with lipase or amylase elevation was similar in each group.

Table 71. New-Onset Grade 3/4 Laboratory Abnormalities

Table 12-10 **Summary of new onset, on-treatment grade 3/4 laboratory abnormalities, from baseline to Week 52 and Week 52 to End of Study - Safety population**

Laboratory test	Lamivudine N=165	Telbivudine N=167
Baseline to Week 52		
ALT (SGPT)	15 (9.1)	9 (5.4)
AST (SGOT)	11 (6.7)	9 (5.4)
Creatine Kinase (CK)	5 (3.0)	14 (8.4)
Lipase	1 (0.6)	3 (1.8)
Neutrophils, Abs	1 (0.6)	0
Platelet Count	3 (1.8)	0
Prothrombin time	0	2 (1.2)
Post-Week 52 to End Of Study		
ALT (SGPT)	19 (11.5)	6 (3.6)
Amylase	0	1 (0.6)
AST (SGOT)	14 (8.5)	4 (2.4)
Creatine kinase (CK)	1 (0.6)	7 (4.2)
Lipase	2 (1.2)	1 (0.6)
Prothrombin time	1 (0.6)	0
Total bilirubin	4 (2.4)	0

Grade 1 or 2 laboratory abnormalities showed similar patterns. Grade 1 or 2 CK elevation was reported in 62% telbivudine vs. 20% lamivudine recipients in the first year of the study, and in 67% telbivudine vs. 23% lamivudine recipients in the second year of the study. Grade 1 or 2 ALT elevation was reported in similar proportions of telbivudine and lamivudine recipients in the first year (44.3% vs. 43.6%, respectively), and in approximately twice the proportion of lamivudine patients in the second year of the study (9.6% telbivudine, 18.2% lamivudine).

Vital Signs

No significant changes in mean and median heart rate and systolic and diastolic blood pressure were observed over the two year treatment period in either treatment group.

Electrocardiograms

Electrocardiograms were not performed in this study.

Common Adverse Events

Overall, 100/165 (60.6%) lamivudine- and 108/167 (64.7%) telbivudine-treated patients experienced at least one adverse event over the 2 year treatment period. Adverse events were more common in the first than in the second year of the study in both treatment groups. Common adverse events are shown in the following table.

Table 72. Common (≥ 2% in either treatment group) Adverse Events from Baseline to End-of-Study

Adverse Event (Preferred Term)	Lamivudine N=165 n/N (%)	Telbivudine N=167 n/N (%)
Patients reporting any AE	100 (60.6)	108 (64.7)
Nasopharyngitis	46 (27.9)	**60 (35.9)**
Fatigue	11 (6.7)	**15 (9.0)**
Hepatitis B	14 (8.5)	6 (3.6)
Upper respiratory infection	10 (6.1)	9 (5.4)
Perihepatic discomfort	**9 (5.5)**	6 (3.6)
Diarrhea	7 (4.2)	6 (3.6)
Abdominal distension	5 (3.0)	**7 (4.2)**
Hepatic pain	**8 (4.8)**	3 (1.8)
Abdominal pain, upper	5 (3.0)	**7 (4.2)**
Pharyngitis	**7 (4.2)**	3 (1.8)
Cough	3 (1.8)	**5 (3.0)**
Blood CK increased	1 (0.6)	**6 (3.6)**
Headache	3 (1.8)	4 (2.4)
Pyrexia	4 (2.4)	3 (1.8)
Gastritis	**5 (3.0)**	1 (0.6)
Toothache	1 (0.6)	**4 (2.4)**

Source: Table 14.3.1.3.1.10 Study Report

Medical Officer Comments: *Adverse events which were more common among telbivudine patients included nasopharyngitis, fatigue, abdominal distension, upper abdominal pain, cough, increased CK, and toothache. AEs more common among lamivudine recipients were upper respiratory tract infection, perihepatic discomfort, hepatic pain, pharyngitis, and gastritis.*

Drug-Related Adverse Events

Adverse events considered at least possibly related to study medication by the investigator were reported in 11/167 (6.7%) lamivudine and in 21/167 (12.6%) telbivudine recipients. Drug-related adverse events reported in at least 2 patients in either treatment group are shown in the following table.

Table 73. Drug-Related Adverse Events

Adverse Event (Preferred Term)	Lamivudine N=165	Telbivudine N=167
Fatigue	2 (1.2)	**3 (1.8)**
Hepatitis B	**3 (1.8)**	2 (1.2)
Blood CK increased	1 (0.6)	**5 (3.0)**
ALT increased	0	**2 (1.2)**
Pain in extremity	0	**2 (1.2)**
Headache	0	2 (1.2)

***Medical Officer Comments**: Almost twice as many patients had adverse events considered drug-related in the telbivudine than in the lamivudine treatment group. The only drug-related event more common in the lamivudine treatment group was hepatitis B. However, the investigator's assessment of drug-relatedness is highly subjective, and these data should only be used in conjunction with other safety data to attribute an adverse event to the study drug.*

Less Common Adverse Events

Adverse events which were reported in 1 to < 2% patients in the telbivudine treatment group included tinnitus (3 patients), nausea (3), gingivitis (3), gastric ulcer (2), pyrexia (3), chest pain (2), hepatic pain (3), pharyngitis (3), skin laceration (2), increased ALT (3), decreased appetite (3), anorexia (2), arthralgia (2), back pain (2), myalgia (2), pain in extremity (2), hypoaesthesia (2), sleep disorder (2), insomnia (2), epistaxis (3), pharyngolaryngeal pain (2), pruritus (2), hypertension (2). In the lamivudine group, adverse events reported in 1 to < 2% patients included nausea (3 patients), abdominal discomfort (2), abdominal pain (2), dyspepsia (2), vomiting (2), tonsillitis (2), urinary tract infection (2), skin laceration (2), contusion (2), heat stroke (2), arthralgia (2), back pain (2), myalgia (2), headache (3), dizziness (3), memory impairment (2), sleep disorder (3), cough (3), pharyngolaryngeal pain (2), pruritus (3), alopecia (2). Adverse events which occurred in < 1% patient (i.e. in one patient) and were consistent with the known safety profile of telbivudine included polymyositis and muscular weakness.

Discussion of Safety Findings in Study 015

The most common adverse events reported with telbivudine treatment were nasopharyngitis and fatigue, and with lamivudine, nasopharyngitis and hepatitis B exacerbation. Adverse events which were more common among telbivudine patients included nasopharyngitis, fatigue, abdominal distension, upper abdominal pain, cough, increased CK, and toothache. The proportion of patients with adverse events resulting in treatment discontinuation was similar in the two treatment groups. The adverse events resulting in telbivudine discontinuation or interruption were pain in extremity, fatigue, hepatic pain, and gastroenteritis.

The proportion of patients with serious adverse events was somewhat higher in the lamivudine than telbivudine group in this study. Serious adverse events of hepatitis B exacerbation were more common in the lamivudine group. One serious adverse event of polymyositis was reported in the telbivudine group. Musculoskeletal adverse events occurring within 30 days of a CK

elevation (grade 1-4) were reported in the telbivudine group but not in the lamivudine treatment group. No other cases of myopathy or myositis were reported in this study. Additionally, no cases of peripheral neuropathy were reported in this study. ALT flares on-treatment were reported in similar proportions of patients in each treatment group; while in a subset of patients who did not continue treatment in the follow-on 022 Study, 14% lamivudine and 0% telbivudine patients had ALT flares during the 4 month post-treatment period. The proportion of patients with Grade 3 or 4 CK elevations was higher in the telbivudine group; while the proportion of patients with Grade 3 or 4 ALT or AST or bilirubin elevation was higher in the lamivudine treatment group in this study.

None of the clinical trial sites for this study were FDA-inspected, and thus assessment of data quality and integrity in this trial cannot be assumed. Thus, even though the study designs were similar for 007 and 015, pooled safety data from these two studies will not be included in the final product labeling.

5.3.3. Study NV-02B-018

This was a randomized, open-label trial of telbivudine vs. adefovir dipivoxil in adults with HBeAg-positive, compensated chronic hepatitis B. Patients were randomized 1:1:1 to telbivudine (600 mg daily), adefovir (10 mg daily), or adefovir (10 mg daily) for 24 weeks followed by telbivudine (600 mg daily) for 28 weeks in the latter group (adefovir-telbivudine "switch" group). Target enrollment was 120 patients (40 per treatment group). The study was performed at 16 clinical trial sites (9 in Asia/Pacific; 2 in Europe, and 5 in North America). The primary objective of the study was to compare antiviral efficacy of telbivudine to adefovir at Week 24 in treatment-naïve adults with chronic hepatitis B. Secondary objectives included comparison of Week 52 efficacy and safety, to assess the relationship between antiviral effect at week 24 and clinical efficacy at Week 52; and as a post-hoc analysis, to characterize frequency of virologic breakthrough and associated treatment-emergent HBV genotypic resistance over the 52 week treatment period. Patients 18-70 years old with clinical history of compensated chronic HBV, with detectable HBsAG, HBeAg-positive, elevated ALT (1.3-10 x ULN), and HBV DNA $\geq$ 6 log10 copies/mL were included in the study. Criteria for exclusion were co-infection with HIV, HCV or HDV, receipt of lamivudine or any investigational anti-HBV nucleoside or nucleotide analog at any time, interferon treatment for HBV within 12 months, hepatocellular carcinoma, and signs of hepatic decompensation.

Most patients enrolled in the study were male (76% overall), and Asian (92%) with a mean age of 32.4 years. Only two patients in this study had been previously treated with interferon for hepatitis B.

The primary efficacy endpoint was reduction in serum HBV DNA (log_{10} copies/mL) at week 24. The primary analysis population was the ITT population (all randomized patients who received at least one dose of study drug with at least one post-baseline observation). At week 24, the telbivudine treatment group had a larger mean reduction in HBV DNA (-6.292 log_{10} copies/mL) from baseline than the combined adefovir and adefovir plus telbivudine treatment group (- 4.919 log_{10} copies/mL). Note that at week 24, patients enrolled in the adefovir plus telbivudine group would have received only telbivudine to that point.

Medical Officer Comments: *This study was not reviewed in detail for efficacy for this efficacy supplement because it was a small, open-label study in similar population to that evaluated in the pivotal study 007 (adult, compensated, chronic hepatitis B), the lack of histological evaluation at study entry and as an outcome measure, and a primary endpoint evaluated at 24 weeks.*

Safety Outcomes in Study 018

The safety population was the ITT population (all randomized patients who received at least one dose of study drug with at least one post-baseline observation). The following are the definitions for the time periods analyzed in safety assessment:

On-Treatment: Time period starting on date of first dose of study medication and ending on the date of the last dose of study medication plus 7 days.

Post-Treatment: Time period starting on Day 8 post-dose through the follow-up period (4 months) for patients electing not to participate in the follow-up study NV-02B-022.

Study Drug Exposure
Patients received telbivudine 600 mg daily for 52 weeks, 10 mg adefovir for 52 weeks or 10 mg adefovir for 24 weeks followed by 600 mg telbivudine for 28 weeks. Dosage modifications were not permitted. The majority (93-96%) of patients in each of the treatment groups received > 360 days study medication.

Patient Disposition
As summarized in the following table, most patients completed the 52 week study; while 4 patients discontinued (2 in telbivudine and 2 in adefovir group). No patients discontinued due to an adverse event.

Table 74. Patient Disposition to Study Week 52

Table 10-1 Patient disposition – n (%) of patients (ITT population)

Parameter	ADV	LdT	ADV/LdT
Number of Patients in the ITT Population	44	45	46
Number of Patients Who Completed the Study	42 (95)	43 (96)	46 (100)
Number of Patients Who Discontinued Study	2 (5)	2 (4)	0
Reason for discontinuation			
Non-Compliance	2 (5)	0	0
Pregnancy	0	1 (2)	0
Adverse Event	0	0	0
Clinical and Biochemical Signs of Hepatic Insufficiency	0	0	0
Signs of Renal Insufficiency	0	0	0
Death	0	0	0
Patient, Investigator, or Sponsor request	0	1 (2)	0

Source: Table 10-1 Study Report

Summary of Adverse Events

As summarized in the following table, a higher proportion of patients experienced at least one adverse event in the telbivudine arm than in the adefovir or adefovir-telbivudine "switch" arm before and after Week 24. The proportion of patients with serious adverse events was similar among treatment groups. No deaths or discontinuations due to adverse events were reported.

Table 75. Summary of Adverse Events in Study 018

	Baseline to Week 24		Post-week 24		
Parameter	Telbivudine N= 45 n/N (%)	Adefovir and Adefovir-Telbivudine Switch Group N= 90 n/N (%)	Telbivudine N=45 n/N (%)	Adefovir N=44 n/N (%)	Adefovir-Telbivudine Switch Group N=46 n/N (%)
Patients with any on-treatment AE	27 (60)	49 (54)	23 (51)	18 (41)	21 (46)
Patients with Drug-related AE	4 (9%)	11 (12%)	3 (7)	3 (7)	3 (7)
Patients with Moderate to Severe AE					
Patients with SAE	0	1 (1)	1 (2)	2 (5)	0
Deaths	0	0	0	0	0
Patients with Discontinuation due to AE	0	0	0	0	0

On-Treatment: time period from first dose of study medication ending on day of last dose of study medication plus 7 days

Deaths
No deaths were reported in this study.

Serious Adverse Events
One patient experienced an SAE, a hand fracture in the adefovir or adefovir-telbivudine switch group prior to week 24. After the week 24 visit, 1/45 telbivudine recipient and 2/44 adefovir recipients experienced serious adverse events. SAEs included tonsillitis (telbivudine), hepatitis B (adefovir), and benign thyroid neoplasm (adefovir). There was one post-treatment SAE in the telbivudine group, an elective pregnancy termination. None of the adverse events were considered drug-related.

Medical Officer Comments: *Narrative summaries for the SAEs were reviewed and it is agreed these SAEs were not likely related to study medication.*

Discontinuations due to Adverse Events
There were no discontinuations due to adverse events in this study.

Moderate to Severe Adverse Events
Analysis of the adverse events dataset for this study revealed that no Grade 4 adverse events were reported in this study. The proportion of patients with adverse events of Grade 1-3 are

shown in the following table. Grade 3 events were uncommon in all treatment groups. Grade 3 adverse events in the telbivudine group included tonsillitis, keratitis, and hepatic steatosis (1 patient each); in the adefovir group 1 patient experienced a Grade 3 thyroid nodule; and in the adefovir/telbivudine group, 1 patient experienced a Grade 3 muscle cramp.

Table 76. Adverse Events by Severity (baseline to end-of-study)

Toxicity Grade	Telbivudine N=45 n/N (%)	Adefovir N=44 n/N (%)	Adefovir/telbivudine N=46 n/N (%)
Grade 1	34 (75.5)	26 (59)	28 (60.9)
Grade 2	7 (16.9)	12 (27.2)	9 (19.6)
Grade 3	3 (6.7)	1 (2.3)	1 (2.2)
Grade 4	0	0	0

Medical Officer Comment: *In this study, 2 cases of hepatic steatosis were reported in the telbivudine group and 1 in the adefovir group. Hepatic steatosis is an adverse event which has been associated with nucleoside/tide analogs. A Boxed Warning for this class effect is found on all approved nucleosides/nucleotides for treatment of HBV.*

Significant Adverse Events

CK elevations
CK was not measured on a routine basis in this study, although CK was measured in some patients who experienced musculoskeletal adverse events. These are discussed below.

Medical Officer Comments: *Not measuring CK routinely in this study, given the known safety profile of telbivudine, is a shortcoming of this study.*

Myopathy and other Musculoskeletal Adverse Events
One case of myopathy (Grade 1, not serious) was reported at week 52 in a patient treated with telbivudine. CK was minimally elevated at that time (253 IU/L, 195 ULN). Myopathy in this case was not considered related to telbivudine. This patient rolled over into the 022 study, and the adverse event was reportedly ongoing. Back pain was the most frequently reported musculoskeletal adverse event in the telbivudine treatment group, and it was more common than in the adefovir or adefovir/telbivudine groups. One patient experienced myalgias in the telbivudine group, CK at that time was reported as 597 and 627 IU/L (ULN 195 IU/L). A summary of the musculoskeletal adverse events in this study is shown in the following table.

Table 77. Musculoskeletal Adverse Events in Study

Adverse Event (preferred Term)	Telbivudine N=45 Number of AEs	Adefovir N=44 Number of AEs	Adefovir/Telbivudine N=46 Number of AEs
Back pain	7	4	3
Myopathy	1	0	0
Myalgia	1	0	3
Musculoskeletal chest pain	1	0	0
Arthralgia	1	2	2
Neck pain	0	0	1
Fasciitis	0	1 (described as right flank "fasciitis"	0

Source: Adverse event Dataset for study 018, from Musculoskeletal and Connective tissue Disorders SOC

Medical Officer Comments: *It is not clear whether back pain, which is a common event, is truly related to telbivudine by virtue of its frequency. The number of patients and musculoskeletal adverse events in this study was relatively small, so no firm conclusions can be drawn.*

Peripheral Neuropathy
No cases of peripheral neuropathy, or symptoms of neuropathy such as hypoaesthesia, paraesthesia were reported in this study.

Lactic Acidosis
No cases of lactic acidosis were reported in this study

ALT Flares
Based on the AASLD definition of ALT (hepatitis) flares (ALT > 2 x baseline and > 10 x ULN), 2 patients experienced ALT flares in the first 24 weeks of the study (1 in the telbivudine group, and 1 in the adefovir or adefovir/telbivudine group); and no patients experienced an ALT flare from week 24 through the treatment period.

In the post-treatment period, 1 patient in the adefovir/telbivudine treatment group experienced an ALT flare after stopping telbivudine, based on the AASLD criteria.

Renal Toxicity
Renal toxicity was defined as an increase in serum creatinine of ≥ 0.5 mg/dL from baseline confirmed by two consecutive laboratory assessments. Note that for inclusion in this study patients were to have a normal creatinine. One patient in the adefovir group had on-treatment renal toxicity; while two patients in the adefovir group had "potential renal toxicity" defined as an increase in creatinine of ≥ 0.3 mg/dL from baseline. No cases of potential renal toxicity or renal toxicity were reported in the telbivudine or adefovir/telbivudine treatment groups.

Medical Officer Comments: *Renal toxicity with adefovir is considered part of its known safety profile.*

Common Adverse Events

As noted above, 60% telbivudine-treated patients and 54% of adefovir or adefovir/telbivudine-treated patients experienced at least one on-treatment adverse event to study Week 24. Adverse events which occurred in ≥ 4% of patients in either treatment group are shown in the following table. The most common adverse events among telbivudine recipients were back pain, diarrhea, and upper respiratory infection; and among adefovir recipients were upper respiratory infection influenza, and abdominal pain.

Table 78. Common (≥ 4%) Adverse Events occurring up to Week 24

Table 12-2 On-treatment adverse events starting on or before the Week 24 visit by preferred term in decreasing frequency occurring in ≥4% of patients in any treatment group

	LdT N = 45 n (%)	ADV and ADV/LdT N = 90 n (%)
Patients with AE(s)	27 (60)	49 (54)
Preferred term		
Back pain	5 (11)	3 (3)
Diarrhoea	5 (11)	3 (3)
Upper respiratory tract infection	5 (11)	7 (8)
Influenza	4 (9)	7 (8)
Headache	3 (7)	5 (6)
Epigastric discomfort	2 (4)	0
Fatigue	2 (4)	4 (4)
Hordeolum	2 (4)	0
Toothache	2 (4)	1 (1)
Abdominal pain (upper)	1 (2)	7 (8)
Arthralgia	1 (2)	4 (4)
Nasopharyngitis	0	4 (4)

Source: Table 12-2 Study Report

On-treatment adverse events after week 24 in this study were reported in 18/44 (41%) adefovir recipients, 23/45 (51%) telbivudine recipients and 21/46 (46%) adefovir/telbivudine recipients. The most common (≥ 4%) adverse events during this time frame are shown in the following table. In the telbivudine group, the most common adverse events were gastritis, malaise, in the adefovir group, upper respiratory tract infection, hepatitis B, and pharyngolaryngeal pain, and in the adefovir/telbivudine switch group upper respiratory tract infection, headache and cough.

Table 79. Common (≥ 4%) Adverse Events occurring after Week 24

Table 12-3 On-treatment adverse events starting after Week 24 visit by preferred term in decreasing frequency, occurring in ≥4% of patients in any treatment group

	ADV N = 44 n (%)	LdT N = 90 n (%)	ADV/LdT N = 46 n (%)
Patients with AE(s)	18 (41)	23 (51)	21 (46)
Preferred term			
Gastritis	0	3 (7)	0
Malaise	0	3 (7)	1 (2)
Abdominal pain	0	2 (4)	0
Abdominal pain (upper)	1 (2)	2 (4)	0
Headache	1 (2)	2 (4)	3 (7)
Hepatic steatosis	1 (2)	2 (4)	0
Nausea	1 (2)	2 (4)	0
Back pain	2 (5)	1 (2)	1 (2)
Cough	0	1 (2)	4 (9)
Diarrhoea	1 (2)	1 (2)	2 (4)
Nasopharyngitis	1 (2)	1 (2)	2 (4)
Pharyngolaryngeal pain	2 (5)	1 (2)	1 (2)
Alopecia	0	0	2 (4)
Hepatitis B	2 (5)	0	0
Upper respiratory tract infection	2 (5)	0	3 (7)

Source: Table 12-3 Study Report

Drug-Related Adverse Events

Adverse events considered at least possibly or reasonably related to study medication by the clinical investigator were reported in 4/45 (9%) telbivudine, and 11/90 (12%) adefovir patients up to study week 24. In the telbivudine group, these events included palpitations (1), diarrhea (1), frequent bowel movements (1), fatigue (1), feeling abnormal (1), and back pain (1). In the adefovir group, these events included upper abdominal pain (3), diarrhea (1), abdominal pain (1), loose stools (1), nausea (1), fatigue (2), asthenia (1), excoriation (1), road traffic accident (1), decreased appetite (1), headache (2), exertional dyspnea (1) and pruritus (1).

Adverse events considered drug-related after week 24 were reported in 3/44 (7%) adefovir, 3/45 (7%) telbivudine, and 3/46 (7%) adefovir-telbivudine switch patients. In the adefovir group, these events included diarrhea (1), nausea (1), hepatic steatosis (1), and hepatitis B (1). In the telbivudine group, these events included nausea (1), myalgia (1), and polymenorrhea (1). In the adefovir to telbivudine switch group diarrhea (1), headache (1), alopecia (1) and dry skin (1) were reported as drug-related in the post-24 week on-treatment period.

Medical Officer Comments: *Assessment of relationship of an adverse event by the investigator is highly subjective, and should only be used to confirm other safety data suggesting a relationship of the adverse event to study drug. These data are especially difficult to interpret in an open-label study.*

Laboratory Abnormalities

Grade 3 or 4 laboratories on-treatment were reported in 2 patients in this study, absolute neutrophil count was decreased in 1 telbivudine recipient (Grade 3: ANC 2.14 at baseline and 0.67 at week 8), and 1 adefovir-telbivudine switch recipient (Grade 4: ANC was 3.10 at baseline and 0.16 at week 4). The latter patient would have been receiving adefovir alone at the time of the Grade 4 laboratory abnormality.

On-treatment (as defined above) Grade 1 or 2 laboratory abnormalities are summarized in the following table. The proportion of patients who experienced a Grade 1 or 2 laboratory abnormality was somewhat higher in the telbivudine group than the other two treatment groups.

Table 80. Grade 1/2 Laboratory Toxicities

Table 12-8 Summary of On-Treatment Grade 1/2 Laboratory Toxicities Safety Population

Laboratory Parameter	Statistic	ADV N = 44	LdT N = 45	ADV/LdT N = 46
Number of Patients Experiencing a Post-Baseline, On-Treatment, Grade 1 or 2 Laboratory Abnormality	n (%)	29 (66)	33 (73)	32 (70)
Hemoglobin (g/dL)	n (%)	0	0	0
WBC count (x10^3/uL)	n (%)	0	0	1 (2)
Absolute Neutrophils (x10^3/uL)	n (%)	7 (16)	4 (9)	5 (11)
Platelets (x10^3/uL)	n (%)	0	1 (2)	1 (2)
Prothrombin Time (s)	n (%)	7 (16)	7 (16)	14 (30)
Phosphate (mg/dL)	n (%)	9 (20)	3 (7)	8 (17)
Creatinine (mg/dL)	n (%)	2 (5)	1 (2)	0
AST (IU/L)	n (%)	13 (30)	18 (40)	8 (17)
ALT (IU/L)	n (%)	14 (32)	16 (36)	8 (17)
Albumin (g/dL)	n (%)	0	0	0
Total Bilirubin (mg/dL)	n (%)	6 (14)	5 (11)	3 (7)
Creatine Kinase (IU/L)	n (%)	0	2 (4)	0
Urine Protein	n (%)	1 (2)	5 (11)	6 (13)

Source: Table 14.3.1.4.3

Note: Patients are counted only once during the period of interest for the given parameter.

Note: Percentages are based on the number of patients in the safety population in each treatment group.

Medical Officer Comments: *The most frequent Grade 1 or 2 laboratory abnormalities in the telbivudine and adefovir groups were AST and ALT elevation; while in the adefovir-telbivudine switch group the most common Grade 1 or 2 laboratory abnormality was PT elevation. On review of the laboratory dataset for this study, all of the PT elevations were Grade 1 with the exception of 1 Grade 2 elevation in an adefovir patient. Grade 1 or 2 proteinuria was more frequently reported in the telbivudine and adefovir/telbivudine groups.*

5.3.3. Study NV-02B-028

This was a phase 1, open-label, multiple-dose study to evaluate the pharmacokinetic interaction between telbivudine and tenofovir disoproxil fumarate (TDF) in healthy subjects. Please refer to Dr. Jenny Zheng's Clinical Pharmacology and Biopharmaceutics review of this study. No significant pharmacokinetic interaction was found between telbivudine and TDF.

Safety results provided with the Study report are briefly reviewed in this section. Telbivudine was administered as a 600 mg tablet and TDF as a 300 mg tablet. Subjects in group 1 received telbivudine 600 mg/day on Days 1-7, followed by telbivudine 600 mg/day plus TDF 300 mg/day on Days 8-14. In Group 2, subjects received TDF 300 mg/day alone for Days 1-7, followed by TDF 300 mg/day plus telbivudine 600 mg/day for Days 8-14. Among 16 healthy subjects enrolled, no deaths, serious adverse events or discontinuations due to adverse events were reported in this study.

Major Inclusion Criteria:
1. Male and female subjects between 19 and 65 years old with body weight within 15% normal body weight relative to height and frame size
2. Normal renal function
3. Hemoglobin $\geq$ 12 g/dL
4. No clinically significant abnormalities as assessed by medical history, physical examination, 12-lead ECG and clinical laboratory testing
5. Female subjects had to be surgically incapable of pregnancy, postmenopausal for at least 1 year, or practicing an acceptable double-barrier method of birth control
6. Subjects must agree not to take OTC medications or prescription medications except any systemic contraceptives within 2 days prior to screening
7. Subjects must agree not to consume alcohol within 2 days of screening
8. Subjects must agree not to take caffeine or xanthine-containing substances or grapefruit juice within 2 days of screening

Major Exclusion Criteria:
1. Subjects with a history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition that, in the opinion of the Principal Investigator, jeopardized the safety of the subject or impact the validity of the study results.
2. Participated in a clinical drug study during the preceding 4 weeks.
3. Donated blood in the past 56 days, or plasma in the past 7 days, prior to study drug administration.
4. Positive screen for HBsAg, anti-HCV, or anti-human immunodeficiency virus (HIV).
5. Pregnant females or females who were breast-feeding.
6. Abused alcohol or illicit drugs, or a history of alcohol abuse or illicit substance abuse within the preceding 2 years. For the purposes of the present study, alcohol abuse was arbitrarily defined as frequent consumption of alcoholic beverages with an average daily intake of more than 40 g of alcohol.
7. Positive screen result for drugs of abuse (including cocaine and its metabolites, opiates, tetrahydrocannabinol (THC), benzodiazepines, amphetamines, phencylclidine (PCP), and

barbiturates) or alcohol during screening or Day -1.

Schedule of Procedures

Patients were followed for 15 days, and the following procedures and assessments were performed as shown in the tables below.

Table. 81. Schedule of Evaluations (Group 1)

Table 9-2 Schedule of observations (Group 1)

STUDY DAY⇨ EVENTS⇩	-21 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 or early termination
Informed Consent	X																
Medical/Medication History Update	X	X															
Assessment of Eligibility	X																
Demographics	X																
Physical Examination	X																X
12-lead ECG	X																
Vital Signs	X		X[1,2]						X[1,2]							X[1,2]	X
Serum Chemistry and Hematology	X[3]		X[2,3]						X[2,3]							X[2,3]	X[3]
Urinalysis (dipstick)	X																X
CL_{cr} (≥ 80 ml/min)	X																
HIV, HBV and HCV Screen	X																
Urine Drug / Alcohol Screen	X	X															
Serum Pregnancy Test	X	X															
Clinic Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LdT Dosing[4]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TDF Dosing[4]										X	X	X	X	X	X	X	
Intensive Pharmacokinetics[5]									X								X
Trough Level Monitoring[6]			X[3]				X[3]							X[3]			
Assessment of AEs										X							

1. Pulse and blood pressure only
2. Predose
3. Fasting sample for serum chemistry (See Section 9.1 and Table 9-3 of the protocol (Appendix 16.1.1) for specific tests and frequency).
4. See Section 7.5.1 of the protocol (Appendix 16.1.1) for dosing schedule.
5. Predose (0 hour), 0.5, 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours postdose (Section 8.1.2.1 of the protocol [Appendix 16.1.1]).
6. Troughs: Days 1, 5 - 6, and 12 - 13 for LdT; Days 1 and 12 - 13 for TDF (Section 8.1.2.2 of the protocol [Appendix 16.1.1]).

Source: Table 9-1 of the protocol (Appendix 16.1.1)

Table 9-3 Schedule of observations (Group 2)

STUDY DAY⇨ EVENTS⇩	-21 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 or early termination
Informed Consent	X																
Medical/Medication History Update	X	X															
Assessment of Eligibility	X																
Demographics	X																
Physical Examination	X																X
12-lead ECG	X																
Vital Signs	X		X[1,2]						X[1,2]							X[1,2]	X
Serum Chemistry and Hematology	X[3]		X[2,3]						X[2,3]							X[2,3]	X[3]
Urinalysis (dipstick)	X																X
CL_{cr} (≥ 80 ml/min)	X																
HIV, HBV and HCV Screen	X																
Urine Drug / Alcohol Screen	X	X															
Serum Pregnancy Test	X	X															
Clinic Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LdT Dosing[4]										X	X	X	X	X	X	X	
TDF Dosing[4]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Intensive Pharmacokinetics[5]									X								X
Trough Level Monitoring[6]			X[3]				X[3]							X[3]			
Assessment of AEs										X							

1. Pulse and blood pressure only
2. Predose
3. Fasting sample for serum chemistry (See Section 9.1 and Table 9-3 of the protocol (Appendix 16.1.1) for specific tests and frequency).
4. See Section 7.5.1 of the protocol (Appendix 16.1.1) for dosing schedule.
5. Predose (0 hour), 0.5, 1, 2, 3, 4, 8, 12, 16, 20, and 24 hours postdose (Section 8.1.2.1 of the protocol [Appendix 16.1.1]).
6. Troughs: Days 1, 5 - 6, and 12 - 13 for LdT; Days 1 and 12 - 13 for TDF (Section 8.1.2.2 of the protocol [Appendix 16.1.1]).

Source: Table 9-2 of the protocol (Appendix 16.1.1)

Table 82. Schedule of Laboratory Tests

Table 9-4 Schedule and tests for serum chemistry and hematology

STUDY DAY⇨ TEST S⇩	Days −21 to −2	Days 1, 7 and 14	Day 15 or early termination
Calcium	X		X
Sodium			
Potassium			
Albumin			
Total bilirubin			
Blood glucose			
ALT/AST	X	X	X
BUN	X	X	X
Serum creatinine	X	X	X
Amylase/Lipase	X		X
Hemoglobin, HCT, platelet, WBC, ANC	X	X	X

Medical Officer Comments: *Safety monitoring (adverse events, laboratory abnormalities, ECGs, vital signs) appeared to be adequate, with the exception of lack of CK monitoring in this study.*

Subject Demographics

Among the 16 subjects enrolled, 7 were female, and 9 were male. Median age was 21 years old in dosing group 1 and 33 years old in group 2. In group 1, 6 subjects were Caucasian and 2 were "other" races; while in group 2, 7 subjects were Caucasian and 1 was Hispanic.

Adverse Events

A total of 33 treatment-emergent adverse events in 11 subjects were reported, 28 adverse events were considered mild, and 5 were considered moderate in severity. The following table summarized the adverse events reported in this study.

Table 83. Summary of Adverse Events

Table 12-1 Treatment-emergent adverse events overall summary

Treatment group	Number of subjects with AEs	Number of subjects dosed	Percentage (%) of subjects with AEs	Number of AEs
LdT alone	6	8	75	11
TDF alone	4	8	50	9
Combination	6	16	38	13
Overall	11	16	69	33

Source: Table 21-1, Study Report NV-02B-028

The adverse events reported in the study are shown in the following table. The most common adverse event with telbivudine alone was fatigue; while the most common adverse events with TDF alone were nausea and acne, and with the combination, headache and cough. None of the adverse events were considered severe or life-threatening. Adverse events of moderate severity included headache (2 events- combination), nausea (1 event-TDF alone), joint sprain (1 event-telbivudine), and dizziness (1 event-telbivudine).

Table 84. Adverse Events Reported in Study 028

Adverse Event (SOC and Preferred Term)	Telbivudine alone N=8 n (%)	TDF alone N=8 n (%)	Combination Telbivudine + TDF N=16 n (%)
Gastrointestinal disorders			
Dyspepsia	0	0	1 (6)
Nausea	0	2 (25)	1 (6)
General Disorders and Site Administration			
Energy increased	1 (13)	0	0
Fatigue	2 (25)	0	0
Feeling hot	0	1 (13)	0
Rigors	0	1 (13)	0
Injury, poisoning, procedural complications			
Joint sprain	1 (13)	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (13)	0	0
Back pain	1 (13)	0	0
Muscle cramp	1 (13)	0	0
Nervous system disorders			
Dizziness	1 (13)	0	0
Headache	1 (13)	1 (13)	3 (19)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (13)	1 (13)	3 (19)
Nasal edema	0	0	1 (6)
Paranasal sinus hypersecretion	1 (13)	0	0
Pharyngolaryngeal pain	1 (13)	0	0
Rhinorrhea	0	1 (13)	0
Throat irritation	0	0	1 (6)
Skin and subcutaneous tissue disorders			
Acne	0	2	0
Erythema	0	0	1

n= number of subjects with adverse event
Source: NV-02B-028 Study Report

Medical Officer Comments: *None of these adverse events reported are inconsistent with common symptoms found in a healthy population taking placebo or no medication.*

Clinical Laboratory Abnormalities

Laboratory data was not summarized by the applicant except to state that all mean chemistry and hematology values remained within the reference range at all post-dose time points. The applicant reported an abnormal urinalysis in one female subject (5-10 WBC/hpf and 1+ urine bacteria) at the end-of-study analysis. This subject was lost to follow-up and a repeat urinalysis was not performed; however, this abnormality was not considered to be clinically significant.

Vital signs were measured at screening, prior to dosing on Days 1, 7, 14 and at discharge or early termination. Mean blood pressure and pulse remained within normal range at all post-dose timepoints.

Conclusions regarding Safety in Study 028
In healthy subjects exposed to telbivudine alone and in combination with TDF, no serious adverse events, deaths, or discontinuations due to adverse events were reported in this study. No unexpected or severe adverse events were reported, and the adverse event profile in this study was relatively unremarkable.

6. Integrated Review of Efficacy

This section summarizes efficacy results and conclusions from Study NV-02B-007 and from the supportive Study, NV-02B-015.

6.1 Proposed Indication

The proposed indication for telbivudine is treatment of Chronic Hepatitis B in adults with evidence of chronic viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Study NV-02B-007

1. Primary Endpoint- 52 weeks (primary analysis) and 104 weeks (secondary analysis)

The primary endpoint in this study, Therapeutic Response, was defined as serum HBV DNA < 5 $\log_{10}$ copies/mL and either HBeAg loss or ALT normalization in HBeAg-positive patients; and HBV DNA < 5 $\log_{10}$ copies/mL and ALT normalization in HBeAg-negative patients. The proportion of patients who achieved a Therapeutic Response declined from week 52 to week 104 in both treatment groups in the HBeAg-positive sub-population; and in HBeAg-negative patients treated with lamivudine. In HBeAg-negative patients treated with telbivudine, however, the proportion of patients who achieved therapeutic response increased slightly from week 52 to 104.

As summarized in the following table, in the ITT population, telbivudine was shown to be non-inferior to lamivudine in both the HBeAg-positive and –negative subpopulations at Weeks 52 and 104 for this endpoint, based on a pre-specified non-inferiority margin of -15%. Additionally, telbivudine was superior to lamivudine in the HBeAg-positive subpopulation at week 52, and in HBeAg-positive and –negative subpopulations at Week 104.

Table 85. Therapeutic Response by HBeAg Status in Study 007

Table 11-22 Therapeutic Response at Week 52 (primary efficacy endpoint) and Week 104 by treatment and HBeAg status - ITT population

Population	Lamivudine n/N (%)	Telbivudine n/N (%)	CI*	*P*-value†
Week 52				
HBeAg-positive	310/463 (67.0)	345/458 (75.3)	2.4, 14.2	0.0047
HBeAg-negative	173/224 (77.2)	166/222 (74.8)	-10.6, 5.7	0.5433
Week 104				
HBeAg-positive	223/463 (48.2)	290/458 (63.3)	8.6, 21.6	<0.0001
HBeAg-negative	148/224 (66.1)	172/222 (77.5)	2.9, 19.9	0.0069

Note: Percentages, CIs, and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*95.68% Confidence intervals at both Week 52 and Week 104 following the 3-step procedure.
†Comparison of proportions between treatment groups, controlling for randomization strata
Source: Tables 14.2.1.3 and 14.2.1.5

2. Key Secondary endpoint- histological response at week 52

Histologic response, the key secondary endpoint in this study was defined as at least a 2-point reduction in the Knodell necroinflammatory score with no worsening in Knodell fibrosis score. An improvement in the Ishak Fibrosis score was defined as 1 point or greater reduction in score between baseline biopsy and week 52 biopsy. Telbivudine was found to be non-inferior (and superior) to lamivudine for histologic response at Week 52 in HBeAg-positive patients, and telbivudine was non-inferior to lamivudine for this endpoint in HBeAg-negative patients. No significant difference between treatment groups was observed in Ishak fibrosis score improvement for patients in either HBeAg subpopulation with a baseline Ishak Fibrosis score ≥ 3. Histologic response was not measured at Week 104 in this study.

3. Other important secondary endpoints at weeks 52 and 104

As reviewed by Lau and Bleibel (2008), although the goal of chronic HBV treatment is to stop progression of liver disease and prevent liver failure and development of hepatocellular carcinoma, an important shorter term goal of HBV therapy is maximal suppression of serum HBV DNA to the lowest possible levels. Eradication of HBV is difficult because it can remain latent as covalently closed circular DNA (cccDNA) or integrate into the host genome. Similarly, although HBsAg seroconversion (loss of HBsAg and development of anti-HBsAg) would be considered a marker for HBV disease resolution, this has not been observed commonly in clinical trials. Loss of HBeAg and HBeAg seroconversion has been associated with long-term remission of HBV disease in interferon treatment studies; however the durability of this endpoint in studies of anti-HBV nucleosides and nucleotides has been more variable.

The approved label for telbivudine (10/06) shows selected virologic, biochemical and serologic outcome measures at Week 52. The following table summarized these endpoints at Weeks 52 and Week 104. The mean HBV DNA (log 10 copies/mL) in both HBeAg subpopulations was reduced to a greater extent in telbivudine-treated than lamivudine-treated patients at both time points. A higher proportion of patients achieved undetectable (< 300 copies/mL) HBV DNA by

PCR, in telbivudine-treated than lamivudine-treated patients at both time points and in both HBeAg subpopulations.

ALT normalization, HBeAg loss and HBeAg seroconversion were similar in both treatment groups at week 52, but a somewhat higher proportion of patients achieved these endpoints at Week 104 in the telbivudine than in the lamivudine treatment group. For both telbivudine and lamivudine, the proportion of HBeAg loss and seroconversion increased from week 52 to week 104. These data are summarized in the following table, and support the conclusions regarding telbivudine drawn from the primary efficacy analysis.

Table 86. Virologic, Biochemical, and Serologic Endpoints at Weeks 52 and 104 in Study NV-02B-007

Response Parameter	HBeAg-positive N=921		HBeAg-negative N=446	
	Telbivudine N=458	Lamivudine N=463	Telbivudine N=222	Lamivudine N=224
Week 52				
Mean HBV DNA reduction from baseline (log10 copies/mL) ± SE	-6.45 (0.11)	-5.54 (0.11)	-5.23 (0.13)	-4.40 (0.13)
% Subjects HBV DNA negative by PCR	60%	40%	88%	71%
ALT normalization	77%	75%	74%	79%
HBeAg seroconversion	23%	22%	NA	NA
HBeAg Loss	26%	23%	NA	NA
Week 104				
Mean HBV DNA reduction from baseline (log10 copies/mL) ± SE	-5.74 (0.15)	-4.42 (0.15)	-5.00 (0.15)	-4.17 (0.16)
% Subjects HBV DNA negative by PCR	56%	39%	82%	57%
ALT normalization	70%	62%	78%	70%
HBeAg seroconversion	30%	25%	NA	NA
HBeAg Loss	35%	29%	NA	NA

Another important secondary endpoint, Virologic Breakthrough, defined as HBV DNA ≥1 log10 copies/mL above nadir occurred in a higher proportion of patients treated with lamivudine than telbivudine at Week 48 and 104 in this study. For both treatment groups, the proportion of patients with Virologic Breakthrough increased from Week 48 to Week 104. At Week 48, among HBeAg-positive patients, virologic breakthrough was reported in 71/463 (15.3%) lamivudine-treated, and 27/458 (5.9%) telbivudine-treated patients; while at Week 104 in this subpopulation, virologic breakthrough was observed in 211/463 (45.5%) lamivudine-treated and 131/458 (28.6%) telbivudine-treated patients. Virologic breakthrough rates were also higher in the lamivudine-treated than telbivudine-treated patients at both time points in the HBeAg-negative subpopulation.

Study NV-02B-015

This Chinese registrational study for telbivudine was submitted by the sponsor as a confirmatory study for this NDA. However, because of differences in the primary endpoint, and lack of histologic outcomes, and because none of the clinical trial sites were FDA-inspected, data from this study can only be used as supportive evidence for telbivudine efficacy for this NDA.

The primary endpoint in this study was HBV DNA (log_{10} copies/mL) reduction from baseline at week 52. The following table summarizes HBV DNA reduction in this study measured at weeks 52 and 104. At both time points and in both HBeAg subpopulations, the mean HBV DNA reduction in the telbivudine group exceeded that in the lamivudine group. Mean HBV DNA reduction from baseline was similar in this study to that observed in Study 007 for each of the HBeAg subpopulations.

Table 87. Mean HBV DNA (log_{10} copies/mL) at Weeks 52 and 104 in NV-02B-015 in ITT population

Response Parameter	HBeAg-positive N=921		HBeAg-negative N=446	
	Telbivudine N=147	Lamivudine N=143	Telbivudine N=20	Lamivudine N=22
Week 52				
Mean HBV DNA reduction from baseline (log10 copies/mL) ± SE	-6.33 (0.15)	-5.54 (0.15)	-5.49 (0.38)	-4.72 (0.38)
Week 104				
Mean HBV DNA reduction from baseline (log10 copies/mL) ± SE	-5.47 (0.26)	-3.97 (0.27)	-5.59 (0.51)	-4.20 (0.49)

The key secondary endpoint in this study was Therapeutic Response, defined as HBV DNA < 5 log_{10} copies/mL and either clearance of HBeAg or ALT normalization. This was the primary efficacy outcome measure for Study 007. Therapeutic response in this study at weeks 52 and 104 is summarized in the following table. The proportion of patients who achieved a Therapeutic Response in each treatment group declined from Week 52 to Week 104. Based on a pre-specified non-inferiority margin of -15%, telbivudine was non-inferior (and superior) to lamivudine for this endpoint in the HBeAg-positive subpopulation at Week 52 and 104. In the HBeAg-negative population, telbivudine was non-inferior to lamivudine at both time points, but superior to lamivudine only at Week 52.

Table 88. Therapeutic Response by HBeAg Status in Study 015

Table 11-11 Patients with Therapeutic Response at Week 52 and Week 104 by treatment and HBeAg status - ITT population

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	CI [1]	P-value [2]
Week 52				
Overall	106/165 (64.1)	145/167 (86.9)	(8.0, 37.6)	< 0.0001
HBeAg-positive	88/143 (61.5)	125/147 (85.0)	(13.4, 33.6)	< 0.0001
HBeAg-negative	18/22 (81.8)	20/20 (100)	(1.6, 34.8)	0.0270
Week 104				
Overall	73/165 (44.0)	115/167 (69.0)	(8.2, 41.8)	< 0.0001
HBeAg-positive	58/143 (40.5)	97/147 (66.0)	(14.2, 36.7)	< 0.0001
HBeAg-negative	15/22 (68.2)	18/20 (90.0)	(-2.0, 45.7)	0.0645

[1] 99.9067% 2-sided CI for the difference in the therapeutic response rate between the treatment groups
[2] p-value for treatment group differences controlling for randomization strata; difference between proportions for categorical variables
Note: Percentages, confidence intervals and p-values were calculated using Mantel-Haenszel weighted estimates based on randomization strata:
Source: Table 14.2.1.1, Table 14.2.1.3, Table 14.2.1.5

The following table shows results from other important secondary endpoints in this study Although this study was limited by its relatively small study size, with a very small HBeAg-negative subpopulation, telbivudine was non-inferior to lamivudine for these endpoints in both HBeAg subpopulations, as in study 007.

Table 89. Virologic, Biochemical, and Serologic Endpoints at Weeks 52 and 104 in Study NV-02B-015 in ITT population

Response Parameter	HBeAg-positive N=921		HBeAg-negative N=446	
	Telbivudine N=147	Lamivudine N=143	Telbivudine N=20	Lamivudine N=22
Week 52				
% Subjects HBV DNA negative by PCR	67% N=147	38% N=143	85% N=20	77% N=22
ALT normalization	87% N=142	75% N=135	100% N=18	78% N=18
HBeAg seroconversion	25% N=138	18% N=138)	NA	NA
HBeAg Loss	31% N=138	20% N=138	NA	NA
Week 104				
% Subjects HBV DNA negative by PCR	58% N=147	34% N=143	90% N=20	68% N=22
ALT normalization	73% N=142	59% N=135	95% N=18	78% N=18
HBeAg seroconversion	29% N=138	20% N=138	NA	NA
HBeAg Loss	40% N=138	28% N=138	NA	NA

NA= not applicable

In this study, Virologic Breakthrough, defined as HBV DNA ≥ 1 log10 copies/mL above nadir in the overall population (HBeAg-positive and HBeAg-negative) was proportionately higher in lamivudine- than telbivudine-treated patients at Weeks 48 and 104. At Week 48, 26/165 (15.8%) lamivudine-treated, and 11/167 (6.5%) telbivudine-treated patients had virologic breakthrough. In both treatment groups, the proportion of patients with breakthrough increased from week 48 to 104, with 85/165 (51.7%) reported in the lamivudine group, and 43/167 (25.6%) in the telbivudine group.

Overall Efficacy Conclusions

Overall, telbivudine was found to be effective for treatment of chronic hepatitis B in the pivotal study, NV-02B-007, which was a well-conducted multinational phase 3 study in patients with chronic hepatitis B and compensated liver function. Telbivudine was shown to be non-inferior to lamivudine for treatment of chronic hepatitis B in HBeAg-positive and HBeAg-negative patients based on the primary endpoint, Therapeutic Response and the key secondary endpoint,

histological response at Week 52. Telbivudine remained non-inferior to lamivudine for the Therapeutic Response endpoint at Week 104 (a secondary comparison), but histological response was not measured at that time. Telbivudine was non-inferior to lamivudine at Week 52 and Week 104 for the primary endpoint in HBeAg-positive and –negative subpopulations, and was superior to lamivudine in HBeAg-positive (but not HBeAg-negative) patients at Week 52, and in both HBeAg subpopulations at Week 104. Virological, serological, and biochemical secondary endpoints at Week 52 and 104 support these conclusions regarding telbivudine efficacy. Virologic breakthroughs were reported more frequently in the lamivudine-treated than the telbivudine-treated group at Year 1 and 2; but for both antiviral agents, the proportion of patients with virologic breakthroughs increased from the first to the second year (15% to 46% for lamivudine; and 6% to 29% for telbivudine). Data from the primary and secondary endpoints at Week 52 and Week 104 in the Chinese Study, NV-02B-015 also support these conclusions, although no histological outcome data was available in this study to confirm the virologic, serologic and biochemical endpoints.

6.1.2 Methods/Study Design

Data from Week 52 of the pivotal study, NV-02B-007, a multicenter, randomized, double-blind, active-controlled study of telbivudine vs. lamivudine for treatment of chronic hepatitis B was previously reviewed by Charlene Brown, M.D. On October, 2006, telbivudine was approved based on Week 52 data from that single, large pivotal study which was conducted in Asia, Europe, Oceania, and North America. For the supplemental NDA 22-011 S-001, 104 week efficacy data from this study was submitted for evaluation of longer term safety and efficacy of this drug for treatment of chronic hepatitis B. The 104 week efficacy and safety data from the pivotal study, NV-02B-007 is the major focus of this review. This study compared telbivudine with lamivudine with regard to the primary endpoint, Therapeutic Response, measured at 52 weeks, as well as a number of secondary endpoints including liver histology at 52 weeks, virologic, serologic, and biochemical endpoints at Weeks 52 and 104. Week 104 efficacy endpoints were considered secondary in this study (See Section 5.3.1. Review of NV-02B-007).

Study NV-02B-015, which was considered a confirmatory study by the applicant, was conducted in China. This study was briefly reviewed with regards to efficacy in this section. However, in 015, liver histology was not evaluated as an endpoint; and thus this study was only considered supportive with regards to the 52 and 104 week endpoints evaluated (See Section 5.3.2. Review of NV-02B-015).

Studies NV-02B-007 and NV-02B-015 were not pooled for efficacy analysis because of differences in the studies' primary endpoints, in patient demographics, and in the lack of liver histology outcomes in the latter study. In this section, efficacy data from both studies is summarized, and compared, where feasible.

Study NV-02B-018 was also submitted with this application. This was a randomized, open-label study to evaluate telbivudine vs. adefovir for 24 weeks, followed by a switch to telbivudine after

week 24 in approximately half of patients randomized to adefovir for an additional 24 weeks (telbivudine vs. adefovir vs. adefovir-telbivudine switch) in nucleoside/tide-naïve patients with chronic compensated HBeAg-positive hepatitis B. The primary efficacy endpoint in study 018, reduction of HBV DNA from baseline, was measured at Week 24. Histologic outcomes were not measured in this study. Because this study was small, open-label, with a primary endpoint measured at 24 weeks in a population studied in the pivotal study 007 and the supportive study 015, this study was reviewed primarily for safety rather than for efficacy.

6.1.3 Demographics

See section 5.3 Individual Studies

6.1.4 Patient Disposition

See section 5.3 Individual Studies

6.1.5 Analysis of Primary Endpoint(s)

See section 5.3 Individual Studies

6.1.6 Analysis of Secondary Endpoints(s)

See section 5.3 Individual Studies

6.1.8 Subpopulations

See section 5.3 Individual Studies

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

NDA 22-154 for a telbivudine oral solution for dosing in patients with renal impairment, included population pharmacokinetics simulations of patient data from the renal impairment study, NV-02B-006 to model different daily dosing regimens in this population. These data were reviewed by Dr. Jenny Zheng in her Clinical Pharmacology and Biopharmaceutics review and were found to be acceptable with regard to the proposed dosing for the telbivudine oral solution in renal impairment. See also section 4.4 in this review for summary of Clinical Pharmacology findings. However, on September 19, 2008, the applicant submitted [redacted] b(4) Additional information is needed from the applicant for review by the Clinical Pharmacology Reviewer.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

See section 5.3 Individual Studies

6.1.11 Additional Efficacy Issues/Analyses

Telbivudine Resistance

Please refer to Dr. Sung Rhee's Clinical Microbiology Review for full details regarding virologic failure and emergence of telbivudine resistance in this study. Also see Section 4.4 of this review.

In a paired sequence analysis of baseline and on-treatment samples at Year 1 for Study 007, DAVP virologists, Drs. Sung Rhee and Julian O'Rear found that amino acid substitutions rtL80I/V, rt180M, rtA181T, rtM204I and rt 229W/V were associated with virologic failure with telbivudine therapy. The M204I substitution was considered the primary resistance mutation; while the others were considered secondary. At that time, 46/115 (40%) patients with virologic failure (HBV DNA $\geq$ 1000 copies/mL in patients treated with a minimum of 16 weeks of telbivudine) and available genotypic data had mutations at codon 204 (rtM204). In 37/46 (80%) patients with the rtM204 substitution, the rtM204I variant was detected; while in 9/46 (20%) the rtM204I/V mutation was present. The M204I mutation is associated with in vitro phenotypic resistance ($\geq$ 1000 fold increase in EC_{50}) to both telbivudine and lamivudine; while the rtM204V variant is associated with approximately 20-fold increase in the EC_{50} for lamivudine, but only 1.3-fold increase in EC_{50} for telbivudine.

In their further analysis of resistance in Study 007, the DAVP virology reviewers found that at Year 1, 164/657 (25%) patients treated with telbivudine for at least 16 weeks experienced virologic failure (defined as HBV DNA $\geq$ 1000 copies/mL). Based on available genotypic data from isolates obtained from patients who experienced virologic failure, the probability of developing the rtM204 substitution was 7% (46/657) at Year 1 and 16% (96/598) at Year 2, for a cumulative probability of approximately 22% over 2 years of study. When analyses were performed in the subpopulations based on HBeAg status, the cumulative probability of developing the rtM204 mutation was higher in the HBeAg-positive than the HBeAg-negative population at Years 1 and 2.

Based on Year 2 data, additional amino acid substitutions associated with the M204I mutation in patients with virologic failure on telbivudine included rtV27A, rtL80I/V, rtL82M, rtV173L, rtL180M, rtT184I/S, rtA200V, rtL229F/V/W, and rtR289K. These may be secondary mutations important for viral fitness.

The HBV DNA of 16 subjects developed rtA181S/T amino acid substitutions while receiving telbivudine, and of these, 9 developed the rtM204I/V substitutions simultaneously (n=1) with or subsequent to a rtA181S/T change (n=8). However, the rtA181S/T substitution was no longer detectable in all 8 isolates displaying the subsequent rtM204I/V substitution.

The A181V/T substitution is associated with adefovir resistance. In addition, the rtA181 substitutions, rtA181T in particular, were detected in on-treatment failure isolates to entecavir and lamivudine therapy at varying frequencies.

7. Integrated Review of Safety

Telbivudine was initially approved on October 25, 2006 on the basis of a single, large, multinational study, NV-02B-007, in which telbivudine was found to safe and effective for treatment of chronic hepatitis B in adults treated for 52 weeks. For this supplemental NDA, safety and efficacy of 104 weeks telbivudine for this indication forms the basis of approval. In that study, a total of 680 patients were exposed to telbivudine for a median of 104 weeks. The size of the safety database and duration of exposure in this study is adequate.

Additional supportive safety data on telbivudine was provided from study NV-02B-015, in which 167 Chinese adults with chronic hepatitis B were exposed to telbivudine for a median of 104 weeks. This safety data will not be used in the final product labeling because the proportion of patients with adverse events in this study was somewhat lower than in study 007 for reasons that are not clear. In study 007, 81% telbivudine and 77% lamivudine recipients experienced adverse events; while in study 015, 65% telbivudine, and 61% lamivudine recipients experienced at least one adverse event. Study 015 was conducted exclusively in China, and whether this reflects differences in reporting adverse events in Chinese patients or investigators, or reflects racial differences in the adverse events in this population compared to study 007 is not known. The latter seems less likely given that in Study 007, over 75% participants were of Asian descent, most of whom were Chinese. Additionally none of the clinical trial sites for study 015 were inspected by the FDA to assess the trial conduct or data integrity. Another study, NV-02B-018 in which 45 adult patients with chronic hepatitis B were treated with telbivudine for up to 52 weeks, was submitted with the supplemental NDA. Safety in this study was reviewed, and found to be consistent with the safety findings in Studies 007 and 015.

Additional important safety information was obtained from the 120-Day Safety Update and a review of postmarketing adverse events reported to the AERS database. Important new safety information on telbivudine was identified from these sources. One of the applicant's clinical studies, CLDT600A2406, was recently stopped due to the high incidence of peripheral neuropathy. In that study, adult patients with chronic hepatitis B were treated with telbivudine monotherapy, telbivudine in combination with pegylated interferon-alfa-2a, or pegylated interferon-alfa-2a alone. The risk of peripheral neuropathy in that study appeared to be higher in patients treated with telbivudine plus pegylated interferon-alfa-2a than in patients treated with telbivudine monotherapy. Additionally, the onset of peripheral neuropathy appeared to be more rapid and the neuropathy appeared to be more severe in the combination therapy arm. Peripheral neuropathy will be included in the final product labeling for telbivudine in the Warning/Precautions section. This new safety information will result in the a requirement for a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide to replace the current Patient Package Insert on the part of the applicant.

Safety issues with telbivudine identified in the initial review of the 52 weeks safety data in study 007 included CK elevation, musculoskeletal adverse events, including myopathy associated with CK elevation, and ALT flares, or exacerbations of hepatitis B during treatment. In the 104 week safety data from study 007, no additional safety issues were identified. Myopathy, including myositis and peripheral neuropathy (polyneuropathy) remained uncommon (4/680, 0.6%) in this study population. New-onset CK elevations were more frequent in telbivudine recipients

throughout the 2-year study; and the proportion of telbivudine patients experiencing a Grade 1-4 CK elevation increased somewhat from the first to second year (67% to 71%). The median CK values in telbivudine recipients peaked around Week 52 and stayed constant thereafter.

ALT flares, thought to represent an acute exacerbation of hepatitis in this population, have been described during treatment, as well as following treatment discontinuation with all of the approved drugs for treatment of HBV. In study 007, the majority of ALT flares on-treatment were reported in the first 24 weeks of treatment, and the incidence did not increase over time. Post-treatment ALT flares were identified in approximately 8 % telbivudine-treated patients within a 4 month period after stopping therapy in the subset of patients who did not enroll into the open-label telbivudine Study 022, or those who discontinued Study 007 prematurely. Other hepatic adverse events were reported in similar proportions of telbivudine- and lamivudine-treated patients, and ALT elevations were not associated with increased total bilirubin, which may be a marker for hepatic toxicity, except in case of hepatic failure in a patient who failed telbivudine treatment.

Other adverse events associated with nucleoside analogs, such as lactic acidosis and hepatic steatosis and hepatomegaly were not reported as adverse events during the first or second year of treatment with telbivudine in study 007. However, serum lactic acid and bicarbonate were not routinely measured in this study. Mild pancreatitis, attributed to gallstones, was reported in one telbivudine-treated patient during the first year of study 007. Lactic acidosis (2 cases), and pancreatitis (1 case) have been reported postmarketing with telbivudine. As reported in the 120-Day Safety Update, hepatic steatosis was reported in a recently completed study, NV-02B-004, in 2 patients treated with telbivudine. Additionally, rhabdomyolysis with and without renal failure has been reported in at least two cases during the postmarketing period to date. There were additional cases of possible rhabdomyolysis in the Adverse Event Reporting System (AERS) postmarketing safety database, but the cases were not reported as such. It is notable that hematologic abnormalities, which have been associated with other nucleoside analogs (e.g. zidovudine), have not been associated with telbivudine to date. Additionally, renal impairment, although identified as a potential safety concern with telbivudine based on preclinical studies, has not been associated with telbivudine treatment so far.

7.1 Methods

Safety data from the pivotal study, NV-02B-007, and the supportive study, NV-02B-015 were evaluated separately and as the pooled "major safety population". Safety data from these two studies was reviewed in detail, including all adverse events, severity of adverse events, drug-attributable adverse events, discontinuation due to adverse events, serious adverse events, deaths, other significant adverse events (e.g. myopathy, peripheral neuropathy), and laboratory abnormalities. Data used in this review was from Study Reports, electronic datasets from individual studies, and pooled studies 007 and 015, case report forms, and the 120-Day Safety Update. Detailed safety data from these two studies is found in the Individual Studies (Section 5.3) in this review; while pooled safety data is reviewed in this section. Any differences observed between the individual study data and the pooled safety data will be discussed in this section.

The 52 week safety data from study NV-02B-007 was reviewed previously (see Clinical Review for NDA 22-011, dated 10-25-08). In this review, the cumulative 104-week safety data were reviewed, and week 52 and week 104 safety data were compared. The applicant's study reports were reviewed and confirmed using JMP Statistical Discovery Software (SAS Institute, Inc.) and Narratives for serious adverse events and deaths were reviewed to assess the potential relationship of these events to study medication.

The applicant also submitted safety data from Study NV-02B-018, an open-label study, as supportive safety information. The safety data from this study was not pooled with that from studies 007 and 015, and was reviewed in Section 5.3 Individual Studies.

The 120-Day Safety Update, submitted May 30, 2008, summarized safety information from two recently completed studies, NV-02B-019, and NV-02C-004, and from ongoing studies, NV-02B-011/ CLDT 600A2301, CLDT600A2406, NV-02B-022/CLDT600A2303. The safety update was reviewed in this section for new safety information, particularly in reference to the newly identified safety issue with telbivudine, peripheral neuropathy, as well as to previously identified safety issues, including myopathy/myositis, CK elevation, ALT flares, and other potential safety issues identified in association with nucleosides, such as lactic acidosis, pancreatitis, and hepatic steatosis.

Postmarketing safety data was not submitted with this NDA; however, the applicant referred to the Periodic Safety Update Report-3 (PSUR-3), submitted on October 31, 2007. The PSUR-3 was reviewed for new safety information. Additionally, consultation was obtained with the Office of Safety and Epidemiology (OSE) to evaluate drug usage data, as well as the postmarketing adverse events reported to AERS, with special emphasis on musculoskeletal adverse events, peripheral neuropathy, ALT flares, and to identify other potential safety signals using datamining techniques. The 120-Day Safety Update is reviewed in Section 7.7.

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

For this review, 104 week safety data from Study 007 was the primary source for safety evaluation. Study 015 was reviewed for supportive safety information. Additionally, study 018 was briefly reviewed for safety (52 week data), and study 028, a drug interaction study in healthy subjects was also briefly reviewed for safety. See Section 5.3 Individual Studies for details on study design and conduct. The following table briefly describes the studies used to evaluate safety.

Table 90. Summary of Clinical Studies used to evaluate Safety

Table 1-1 Summary of key and supportive completed studies

Study No.	Study objective, population	Safety population: Comparator(dose) n	Safety population: LdT (600 mg) n	Treatment duration (weeks)
Key studies of major safety population				
[NV-02B-007] (double-blind)	Antiviral & clinical efficacy, safety and tolerability in adults with HBeAg-positive & HBeAg-negative compensated chronic hepatitis B	Lamivudine (100 mg) 367	369	104
[NV-02B-015] (double-blind)	Antiviral & clinical efficacy, safety, and tolerability in Chinese adults with HBeAg-positive & HBeAg-negative compensated chronic hepatitis B	Lamivudine (100 mg) 165	167	104
Supportive safety				
[NV-02B-018] (open-label)	**Antiviral & clinical efficacy, safety, and tolerability in adults with HBeAg-positive compensated chronic hepatitis B**	**Adefovir (10 mg) 44**	**91[1]**	**52**

LdT = telbivudine
[1] number of patients includes patients who received adefovir for 24 weeks, then switched to LdT for 28 weeks.

Source: [NV-02B-007 Wk 104 – Table 14.1.1], [NV-02B-015 Wk 104 – Table 14.1.1], and [NV-02B-018 – Table 14.1.1].

Additional Clinical Studies with Safety Data

The 120-Day Safety Update submitted on May 30, 2008 contained safety information from two recently completed studies, as shown in the following table.

Table 91. Recently Completed Clinical Studies

Table 1-1 Summary of studies providing key safety data in the 120-day safety update

Study No.	Study objective, population	Enrolled/ planned patients	Safety population	Planned treatment duration	Telbivudine dosage	Type of comparator	Cut-off date
NV-02B-019	Assess antiviral efficacy of switching lamivudine-treated patients to telbivudine or continuing lamivudine patients. Population: adults with CHB	248	246	52 weeks	600 mg daily	Lamivudine (100 mg)	Completed
Study No.	**Study objective, population**	**Enrolled/ planned patients**	**Safety population**	**Planned treatment duration**	**Telbivudine dosage**	**Type of comparator**	**Cut-off date**
NV-02C-004	**To compare the antiviral efficacy of the combination of telbivudine + valtorcitabine to telbivudine monotherapy** **Population: adults with CHB**	**134/130**	**132**	**52 weeks**	**600 mg daily**	**Telbivudine (600 mg) + valtorcitabine (750 mg)**	**completed**

NV is Idenix-assigned, CLDT600A is Novartis-assigned study number

The 120-day Safety Update also included safety information from 3 ongoing studies, as shown in the following table.

Table 92. Ongoing Clinical Studies submitted with 120-day Safety Update

Table 1-2 Summary of other clinical studies in 120-day safety update

Study No.	Study objective, population	Enrolled/ Planned patients	Safety population	Planned treatment duration	Telbivudine dosage	Type of comparator	Cut-off date
NV-02B-011/ CLDT600A 2301[1] (double-blind)	To compare antiviral efficacy, safety, and tolerability of telbivudine to lamivudine Population: adults with decompensated CHB	240	232	104 weeks	600 mg	lamivudine	Dec-31-2007
CLDT600A 2406	**Comparing the safety and efficacy of combination telbivudine+ Pegasys® with Pegasys® monotherapy and telbivudine monotherapy** **Population: adults with HBeAg positive CHB**	**159/300**	**152**	**104 weeks**	**600 mg**	**Pegasys® 180ug**	**Feb-29-2008**
NV-02B-022/ CLDT600A 2303[1]	**An Open Label Trial of Telbivudine (LdT) in Adults with CHB Previously Treated in Idenix-Sponsored Telbivudine Studies**	**2100**	**667***	**104 weeks**	**600 mg**	**none**	**Dec-31-2007**

[1]NV is Idenix-assigned study number, CLDT600A is Novartis-assigned study number
* patients enrolled in NV-02B-007 and NV-02B-015 who rolled into NV-02B-022/ CLDT600A2303

Medical Officer Comments: *Note that safety data from study NV-02B-011 remains blinded to study treatment. Note also that study CLDT600A2406 was stopped prematurely due to a safety issue in the combination treatment arm (Pegasys +telbivudine). Initially only the combination arm was stopped by DSMB; however, because the study could not meet its objective, it was stopped on May 15, 2008.*

7.1.2 Adequacy of Data

Adverse events in these studies were coded with MedDRA version 6.1 coding dictionary. Based on comparison of verbatim adverse events and the coded preferred term used in the adverse event datasets, coding appeared to be adequate. Occasionally, some preferred terms were not sufficiently descriptive to provide important information about the event (e.g. arrhythmia). However, this appeared to be a problem at the level of the case report form, because verbatim terms in such cases were the same (i.e. arrhythmia). In some cases, such as myopathic adverse

events, or adverse events consistent with peripheral neuropathy, preferred terms were grouped by the applicant and/or by the reviewer to search for additional similar adverse events.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

The safety data from studies 015 and 007 was appropriate for pooling because they were similar in design, inclusion and exclusion criteria, comparator, study drug dosing regimens. These studies, however, differed in the primary study endpoints, and in patient demographics (i.e. racial distribution). Study NV-02B-015 evaluated only Chinese patients; whereas in study NV-02B-007, the majority of patients were Asian, but other races were included. Pooled safety data was used to estimate incidence of adverse events, serious adverse events, deaths, discontinuations for patients treated with telbivudine in comparison to lamivudine.

Medical Officer Comments: *Although the pooled safety data from these two studies is discussed in this section, we have proposed that only safety data from the 007 study be included in the final product labeling. There are several reasons for not including the pooled safety data in the label: a) the study population in 015 was 100% Chinese; b) In the 015 study, the incidence of patients with any adverse event was lower in both treatment groups than in study 007; c) No FDA inspections were performed on the clinical trial sites for study 015 which was performed exclusively in China, and it is not known whether the lower incidence of adverse events in that study is due to a difference in occurrence of adverse events (e.g. due to racial differences) or to differences in reporting by patients or investigators; d) Although the adverse event profile was similar in the two studies, pooling of these studies diluted the overall incidence of adverse events in the pooled safety population, and the incidence of some specific adverse events (e.g. CK elevation).*

7.2 Adequacy of Safety Assessments

Overall, safety assessment in these studies appeared to be adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The major safety population from studies 007 and 015 include 847 telbivudine-treated patients and 852 lamivudine-treated patients. Patients in these studies all had confirmed chronic hepatitis B (HBeAg-positive or HBeAg-negative) with evidence HBV replication and either persistent elevations in hepatic transaminases or histologically active disease. The majority of patients received 104 weeks of telbivudine 600 mg daily, or 104 weeks lamivudine, 100 mg daily, the approved doses for treatment of HBV. Thus, there were sufficient numbers of patients exposed to the appropriate dose of telbivudine to adequately assess long-term (up to 2 years) safety of this drug. Telbivudine exposure in the major safety population is shown in the following table.

Table 93. Telbivudine Exposure in Major Safety Population

Table 2-2 Duration of exposure (weeks) by treatment – major safety population

	LAM 100 mg	LdT 600 mg	p-value[1]
NV-02B-007	(N=687)	(N=680)	
mean (SE)	99.3 (0.68)	100.2 (0.62)	0.2932
median	104.1	104.1	
minimum, maximum	1, 127	2, 127	
NV-02B-015	(N=165)	(N=167)	
mean (SE)	99.9 (1.0)	101.6 (0.89)	0.2202
median	104.0	104.0	
minimum, maximum	18.9, 106.3	18.1, 106.0	
NV-02B-007/NV-02B-015	**(N=852)**	**(N=847)**	
mean (SE)	**99.4 (0.58)**	**100.5 (0.53)**	**0.1607**
median	**104.00**	**104.14**	
minimum, maximum	**0.6, 126.9**	**2.4, 126.9**	

[1] p-value from t-test
LAM = lamivudine, LdT = telbivudine

Source: Table 2-2 Summary of Clinical Safety

Because the safety population was comprised mainly of persons of Asian descent, there were not adequate numbers of Blacks/African Americans, Hispanics/Latinos, and non-Asian/non-White patients to assess telbivudine safety in these subpopulations. Females comprised approximately 25% of the major safety population in these studies, providing sufficient number of females to allow analysis of safety by gender.

In the phase 3b study, NV-02B-018, a total of 91 patients received at least one dose of telbivudine (the 90 patients for up to 24 weeks, and 43 for up to 52 weeks). Telbivudine exposure in the recently completed studies, 019 and 004 and in the ongoing studies, 022 and 011 are reviewed in Section 7.7.

Demographics in Pooled Major Safety Population

Patient demographics in studies 007 and 015 are described in Section 5.3 Individual Studies. In the pooled safety population, the median patient ages were 33 years (Lam) and 32 years (LdT). The majority (76-77%) patients were male, and of Asian descent (80-82%), as summarized in the table below. Note that Chinese patients make up approximately 55% of the population in the pooled safety database.

Table 94. Demographic Characteristics in Major Safety Population

Table 3-3 Demographics characteristics by treatment – Pooled NV-02B-007/NV-02B-015

	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)	p-value[1]
Age			0.3268
N	852	847	
Mean (SE)	35.0 (0.41)	34.3 (0.40)	
Median	33.0	32.0	
25%, 75%	25.0, 43.0	26.0, 42.0	
min, max	15.0, 66.0	16.0, 68.0	
Gender			0.6408
Male	654 (76.8)	642 (75.8)	
Female	198 (23.2)	205 (24.2)	
Race			0.6812
Caucasian	111 (13.0)	98 (11.6)	
Asian	680 (79.8)	692 (81.7)	
Chinese	532 (62.4)	548 (64.7)	
Korean	47 (5.5)	54 (6.4)	
Thai	51 (6.0)	50 (5.9)	
Japanese	1 (0.1)	0	
Vietnamese	28 (3.3)	27 (3.2)	
Filipino	7 (0.8)	4 (0.5)	
Malay	4 (0.5)	2 (0.2)	
Other	10 (1.2)	7 (0.8)	
African/African American	10 (1.2)	7 (0.8)	
Hispanic/Latino	8 (0.9)	4 (0.5)	
Middle Eastern/Indian Subcontinental	11 (1.3)	14 (1.7)	
Other	32 (3.8)	32 (3.8)	
Height (cm)			0.7844
N	847	844	
Mean (SE)	168.4 (0.28)	168.5 (0.27)	
Median	170.0	169.0	
25%, 75%	163.0, 174.0	163.0, 174.0	
min, max	140.5, 198.0	132.1, 195.6	
Weight (kg)			0.0335
N	851	847	
Mean (SE)	68.1 (0.50)	66.7 (0.48)	
Median	67.0	65.9	
25%, 75%	58.0, 75.3	58.0, 74.9	
min, max	38.0, 149.7	38.0, 126.0	

[1] T-test for continuous variables, chi-square for categorical variables.

Source: Table 3-3 Summary of Clinical Safety

Medical Officer Comments: *Median patient age was somewhat higher in the 007 study (approximately 35 years old) in comparison to the 015 study (approximately 28 years old); and patient weight was somewhat higher in the 007 study (approximately 68 kg) compared to the 015 study (approximately 60 kg).*

7.2.2 Explorations for Dose Response

No dose-response studies were submitted for this supplemental NDA. The telbivudine dose of 600 mg daily used in these phase 3 studies was based on safety and antiviral efficacy data in the original NDA.

7.2.3 Special Animal and/or In Vitro Testing

No new clinical pharmacology or animal toxicity data was submitted with this supplemental NDA. A number of microbiology studies were submitted, including IDIX-07-151, which evaluated Week 104 resistance data from study NV-02B-007, ICIX-07-206 which evaluated clinical predictors of resistance, IDIX-06-140 which evaluated Week 48 resistance data from study NV-02B-015, and IDIX-07-200, which evaluated Week 104 resistance data from Study NV-02B-015. *In vitro* mitochondrial toxicity studies in mouse skeletal muscle (study IDIX 07-116a) and in primary human hepatocytes were submitted in response to Post-Marketing Commitment #13 on March 28, 2008. Please see Dr. Sung Rhee's Microbiology review for analysis of these studies.

7.2.4 Routine Clinical Testing

In general, routine clinical testing and assessment of adverse events was adequate in the pivotal study, NV-02B-007. Study visits were conducted at screening, baseline, and on Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 68, 76, 84, 92, and 100. The end-of-study visit was done at Week 104. Adverse events were assessed at each study visit from baseline to week 104 or early termination visit. Safety laboratory assessments at each visit were appropriate, including liver function tests (AST, ALT, albumin and total bilirubin), as well as creatinine total protein, amylase, lipase, and CK. However, serum lactic acid and/or bicarbonate levels were not routinely assessed in study 007, and thus occurrence of lactic acidosis, an adverse effect associated with other nucleoside/nucleotide analogs on the basis of laboratory assessment could have been missed. Electrocardiograms were not routinely performed in study 007. This was reasonable because a previous thorough QT/QTc study demonstrated no significant risk for QT prolongation with telbivudine.

Post-treatment, patients who discontinued the study prematurely for any reason other than efficacy, or patients who elected not to enter the rollover study, NV-02B-022, were followed with monthly visits for 4 months. Patients who discontinued treatment early because they met criteria for discontinuation due to efficacy were followed through week 104 on the same schedule as those on-treatment.

Routine clinical testing and assessment of adverse events also appeared to adequate in the supportive study, NV-02B-015. Adverse event monitoring and safety laboratory assessments were similar to those performed in study 007.

7.2.5 Metabolic, Clearance, and Interaction Workup

As reviewed for the original NDA 22-011, the preclinical and clinical evaluations of metabolic, clearance, and potential drug interactions were considered adequate for this drug and the indication studied. No new clinical pharmacology information was submitted with NDA 22-011 S-001. However, with NDA 22-154 for the new oral formulation of telbivudine, a clinical pharmacology study, NV-02B-028, which evaluated the PK interaction between tenofovir disoproxil fumarate (Viread®) and telbivudine in healthy subjects. See Clinical Pharmacology and Biopharmaceutics review by Dr. Jenny Zheng for review of the pharmacokinetic data from this study. Safety data from this study is reviewed in Section 5.3 above.

7.27 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events associated with other nucleoside analogs used for treatment of HBV or HIV include lactic acidosis, hepatic steatosis, hepatomegaly, peripheral neuropathy, myopathy or hematological adverse events or laboratory abnormalities was adequate. Additionally, the evaluation for potential liver toxicity was integral to both efficacy and safety assessment in the pivotal and supportive studies for telbivudine.

7. 3 Major Safety Results

In this section, the major safety results from the pivotal study, NV-02B-007 and the supportive study, NV-02B-015 are pooled and analyzed as the "major safety population". Safety in individual studies is reviewed in Section 5.3 Individual Studies. Note that although the safety data from these two studies are pooled and reviewed in this section, the Division has proposed that only safety data from the pivotal study, 007, be included in telbivudine final product labeling as discussed above. The applicant defined 3 time periods for the analysis of adverse events and other safety data. These were defined as follows:

On-Treatment: from baseline to end-of-treatment plus 7 days; and from restarting blinded study treatment to end-of-treatment plus 7 days

Off-Treatment: From 8 days after the end-of-treatment to date of study discontinuation. This time period was applicable only to patients who discontinued treatment due to efficacy during the study.

Post-treatment: From 8 days after the end-of-treatment to date of study discontinuation through the follow-up period of the study. This time period applied mainly to patients who prematurely discontinued from the study or who did not elect to enter the follow-on study, NV-02B-022 after completion of NV-02B-007.

The proportion of patients with any adverse event, serious adverse events, deaths, moderate to severe adverse events, and discontinuations due to adverse events in the pooled safety population in comparison to the clinical individual studies (007 and 015) is summarized in the following table.

Table 95. Summary of Adverse Events in the "Major Safety Population" (Pooled 007/015 Studies):

Parameter	Study 007		Study 015		Pooled Studies 007 and 015	
	Lamivudine N=687 n/N(%)	Telbivudine N=680 n/N(%)	Lamivudine N=165 n/N(%)	Telbivudine N=167 n/N(%)	Lamivudine N=852 n/N(%)	Telbivudine N=847 n/N(%)
Patients with any adverse event	529 (77)	551 (81)	100/165 (60.6)	108/167 (64.7)	630 (73.9)	659 (77.8)
Patients with any drug-related adverse event*	159 (23.1)	197 (29.0)	11 (6.7)	21 (12.6)	171 (20.1)	218 (25.7)
Patients with Moderate-Severe adverse event	187 (27.2)	203 (29.9)	42 (25.5)	36 (21.6)	229 (26.9)	239 (28.2)
Patients with Serious Adverse Event	44 (6.4)	33 (4.9)	11 (6.7)	6 (3.6)	55 (6.5)	39 (4.6)
Deaths	1	0	1 (0.6)	1 (0.6)	2	1
Patients who discontinued treatment due to adverse event	26 (3.8)	27 (4.0)	7 (4.2)	5 (5.0)	33 (3.9)	32 (3.8)
Patients who discontinued treatment due to SAE	7 (1.0)	2 (0.3)	3 (1.8)	2 (1.2)	10 (1.2)	4 (0.5)

*Investigator assessment of relatedness

Medical Officer Comments: *Note that the proportion of patients with any adverse event is lower in the pooled major safety population than in study 007 because of the lower incidence of adverse events in Study 015. Otherwise, the proportion of patients with drug-related adverse events, moderate to severe adverse events, and discontinuation due to adverse events was similar across studies. As discussed above, because Study 015 trial sites were never inspected by the FDA, and because it is unclear why the incidence of adverse events was lower in that study, we have proposed that pooled safety data not be included in the final product labeling.*

7.3.1 Deaths

In the pivotal study, NV-02B-007, one death was reported. The patient was receiving lamivudine, and cause of death was traffic accident, not considered related to study medication. In the supportive study, NV-02B-015, 2 deaths were reported, one in each treatment arm. One patient treated with telbivudine died due to murder; and one patient treated with lamivudine died due to acute exacerbation of hepatitis B. Neither death was considered directly related to study medication. Deaths in these studies are summarized in the following table.

Table 96. Deaths in the Pooled Major Safety Population

Study Number NV-02B-	Patient ID	Study Drug	Onset after Study Drug initiation	Cause of Death	Relationship to study drug	Medical Officer's Assessment of Relationship to Study Drug
007	AUV-70	Lamivudine	8 months	Traffic accident	Not related	Not Related
015	AUV-83	Telbivudine	4 months	Murder	Not related	Not related
015	AUV-212	Lamivudine	Day 470	Acute exacerbation of hepatitis B and death due to hepatic failure	Not related	Pt. also positive for HEV IgG. IgM not reported. Could indicate recent or prior HEV infection.

Medical Officer Comments: *The narrative summaries for the deaths in these studies were reviewed, and it is agreed that none of the deaths appear directly related to study medication. Patient AUV-212 in study NV-02B-015 had a lamivudine treatment failure at week 60 after initial HBV DNA suppression, as evidenced by viral rebound on treatment.*

Deaths in other Completed Studies

Study NV-02B-018: no deaths were reported.

Study NV-02B-019: (from 120-Day Safety Update) 1 death was reported in patient who received lamivudine. This was described as a sudden death presumed to be due to cardiac arrest or pulmonary embolism in 44 year old Tongan male with history of ischemic heart disease, who collapsed during training for a triathathon. The narrative summary for this death was reviewed, and it is agreed that the death was probably not related to study medication.

Study NV-02B-004: no deaths were reported.

Deaths in Ongoing Studies:

Study NV-02B-022: 8 deaths reported to date in this rollover open-label study of telbivudine. Limited information is available regarding these deaths other than two deaths were due to gastrointestinal hemorrhage or esophageal variceal bleeding, both associated with progressive

liver disease. One death was due to septic shock, and one was due to pneumonia with associated sepsis. Two deaths were due to malignant hepatic neoplasm. One death was due to head injury, and one death was due to unknown causes.

Medical Officer Comments: *The narratives for the deaths in Study 022 were reviewed, and this reviewer concurs that none was likely related to telbivudine, and were more likely related to progressive liver disease.*

Study NV-02B-011: As of the cut-off date for the safety update, 232 patients had enrolled in this study. A total of 33 deaths were reported in patients with decompensated liver disease. These data remain blinded to treatment. Causes of death shown in table below.

Table 97. Cause of Death in Study 011 (blinded to treatment) (from safety update)

Center/patient	Study day of last dose	Date of death	Study day of death	Principal cause (preferred term)	
33/007	344		450	Hepatic neoplasm malignant	
34/006	834		470	Gastrointestinal hemorrhage, Jaundice, and Pallor	b(6)
4/006	418		419	Cerebral hemorrhage	
41/007	86		87	Hepatic encephalopathy	
56/002	451		462	Hepatic failure, Ascites, and Hernia	
65/010	845		847	Septic shock	
66/002	466		466	Hepatorenal syndrome	b(6)
71/001	717		717	Pneumonia, Hepatic Coma, and Ascites	
71/008	586		586	Esophageal varices hemorrhage	
76/001	62		62	Hepatic cirrhosis	
80/004	54		57	Sepsis	
84/015	430		432	Sepsis	
85/017	105		106	Esophageal varices hemorrhage	b(6)
86/014	62		64	Enteritis	
86/015	179		183	Depressed level consciousness	
86/017	210		229	Hepatic encephalopathy	
87/009	282		282	Sepsis	
87/018	193		194	Gastrointestinal hemorrhage	
87/029	496		500	Death	b(6)
89/017	9		10	Hepatorenal syndrome	
89/024	35		43	Hemorrhage	

Source: 120-Day Safety Report, May 30, 2008

Medical Officer Comments: *This study is ongoing and remains blinded, but the deaths in this study appear to be consistent with decompensated or end-stage liver disease.*

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events in Study NV-02B-007

On-treatment SAEs were reported in 33/680 (4.9%) patients who received telbivudine, and in 44/687 (6.4%) of those who received lamivudine in this study. See Section 5.3 Individual Studies for review of the serious adverse events in this study.

Serious Adverse Events in Study NV-02B-015
In this study, a total of 11/165 (6.7%) patients treated with lamivudine and 6/167 (3.6%) patients treated with telbivudine experienced a serious adverse event. See Section 5.3 Individual Studies for review of serious adverse events in this study.

Serious Adverse Events in Study NV-02B-018
Serious adverse events in this study were reviewed in Section 5.3 Individual Study Reports.

Serious Adverse Events in Study NV-02B-011
This is an ongoing study of telbivudine vs. lamivudine in patients with decompensated liver disease and the safety results remain blinded to treatment. The applicant submitted narrative summaries for patients with SAEs. These were briefly reviewed, and most could be considered consistent with the underlying disease process, although a few could be potentially related to study medication (e.g. pancreatitis). Because the treatment arm is still blinded in this ongoing study, no conclusions can be drawn regarding the SAEs in this study.

Serious Adverse Events in Study NV-02B-022
This was the rollover study in which patients from studies 007 and 015 could elect to enroll to receive telbivudine in an open-label study. Narratives for all of the serious adverse events to date were provided with this submission, and are summarized below. Note that some patients had multiple SAEs, which are listed separately.

Table 98. Serious Adverse Events in Study 022 (Open-Label Telbivudine)

Patient Number	Adverse Event (Preferred Term)	Gender/age	Action	Outcome	Comments	Investigator's Assessment
001-003	**Myositis/Myopathy**	Female/47	discontinued	continuing	Muscle biopsy showed "extensive rhabdomyolysis"	**Not related**
005-061	Benign hydatidiform mole	Female/28	None	Resolved	Termination of molar pregnancy	Not related
005-107	Atypical chest pain	Female/24	None	Resolved	Mild T-wave inversion on ECG; CK normal	Not related
005-107	Vulvar angiokeratoma (fungal)	Female/59	none	Resolved		Not related
005-107	Urine retention	Female/59	None	Resolved	Secondary to UTI	Nor related
005-107	Malignant hepatic neoplasm	Female/59	None	Continuing	Enrolled from study 011 with decompensated HBV	Not related
008-001	Hepatitis B	Male/31	None	Resolved	Telbivudine discontinued 1 year prior to event	Related
009-008	Peritonitis, bacterial	Male/50	None	Continuing	Enrolled from 011 study with decompensated HBV	Not related
012-001	Arrhythmia (described as sinus bradycardia with sinus arrhythmia)	Male/59	None (telbivudine discontinued prior to event due to efficacy)	Resolved with residual defects	History of possible drug-induced myositis in previous study, history of SVT, VT, paroxysmal afib. Catheterization revealed CAD, later developed SVT.	Not related
012-001	Angina pectoris	Male/59	None	resolved	telbivudine discontinued at some time prior to event due to efficacy	Not related
012-001	Atypical chest pain	Male/59	None	Resolved	telbivudine discontinued at some time prior to event due to efficacy	Not related
012-002	Colon cancer stage 0	Male/52	None	Continuing	Polyp	Not related
012-003	Cerebral hemorrhage	Male/59	None	Resolved, residual effects	History of paroxysmal afib on coumadin	Not related
012-	Anogenital dysplasia;	Male/63	Interrupted	Resolved	Perforation during	Not related

005	and rectal perforation				endoscopic submucosal dissection	
012-005	Acute MI	Male/64	None	Resolved	History of HTN, CAD, hyperlipidemia	Not related
012-007	Dengue fever	Male/27	None	Resolved		Not related
014-022	Deafness	Male/42	Discontinued	Continuing	Also on pegylated interferon-alfa-2a	**Not related**
014-023	Pharyngitis	Male/42	None	Resolved		Not related
014-025	Acoustic neuroma	Female/54	None	Resolved	Radiosurgery	Not related
014-037	Nasal cavity mass	Male/50	None	Resolved	Endoscopic sinus surgery; biopsy revealed chronic inflammatory cell infiltration	Not related
014-040	Diffuse large B-cell lymphoma	Male/35	None	Continuing	No underlying medical conditions	Not related
014-040	Pneumonia	Male/36	Interrupted	Continuing	Receiving chemotherapy, neutropenic	Not related
014-040	ARDS/respiratory failure	Male/36	None	Continuing		Not related
014-040	Leukopenia	Male/36	None	Resolved	G-CSF	Not related
014-040	Septic shock	Male/36	Discontinued	Death	Likely secondary to pneumonia	Not related
016-001	Malignant hepatic neoplasm/ GI hemorrhage	Male/42	None	Death	Likely secondary to pneumonia and septic shock	Not related
036-024	Death	Male/50	Discontinued	Death	GI bleed- not confirmed by autopsy	Not related
064-041	Sepsis	Male/58	None	Death	History of DM; previously enrolled in study 011 study for decompensated HBV	Not related
067-043	Hepatocellular carcinoma	Female/50	None	Death	previously enrolled in study 011 study for decompensated HBV	Not related
106-004	Malignant hepatic neoplasm	Male/55	Discontinued	Death	Previously enrolled in study 007	Not related
125-001	Head injury	Male/60	Discontinued	Death	S/P fall; previous episode of hyperglycemia; previously enrolled in study 011	Not related
014-040	Acute renal failure	Male/36	None	Continuing	See other SAEs for same patient-	Not related

					suspect due to septic shock	
014-041	Malignant hepatic neoplasm	Male/65	None	Resolved	previously enrolled in study 011 study for decompensated HBV; had tumor ablation	Not related
014-043	Esophageal varices	Male/49	None	Resolved	previously enrolled in study 011 study for decompensated HBV	Not related
014-044	Malignant hepatic neoplasm	Female/47	None	Continuing	previously enrolled in study 011 study for decompensated HBV	Not related
014-045	Hemorrhoidal bleeding	Male/35	None	Continuing	previously enrolled in study 011 study for decompensated HBV	Not related
016-001	Hemorrhoids	Male/41	None	Resolved	Hemorrhoidectomy	Not related
016-001	Malignant hepatic neoplasm	Male/42	None	Continuing	Previously enrolled in study 007	Not related
018-017	Hepatitis B	Male/38	Discontinued	Resolved	Started on adefovir and entecavir	Not related
020-004	**Myopathy "necrotizing myopathy"**	Male/64	Discontinued	Continuing	Previously enrolled in study 007; CK elevated	**Related**
022-004	Hyperglycemic hyperosmolar nonketotic syndrome	Female/61	Interrupted	Resolved with residual defects	Glucose 921 mg/dL; lactic acid elevated; acute renal failure; on prednisone for RA;	Not related
024-004	Proteinuria	Male/43	None	Resolved	Renal biopsy showed IgA nephropathy	Not related
024-008	Colon cancer	Male/53	Interrupted	Resolved	Polypectomy; later had hemicolectomy and chemotherapy	Not related
024-010	CAD	Male/60	None	Resolved	History of DM, smoking	Not related
024-022	Adjustment disorder	Female/45	None	Resolved	History of depression	Not related
024-025	Benign pituitary tumor	Male/25	None	Continuing	Previously enrolled in 007 study	Not related
024-028	Malignant hepatic neoplasm	Male/55	Interrupted	Continuing	Previously enrolled in 007 study	Not related
024-028	Post-op wound infection	Male/55	None	Resolved	S/P liver transplant	Not related
024-028	Upper respiratory tract infection	Male/56	Discontinued	Resolved	S/P liver transplant; and also had pancytopenia	Not related

024-028	Sepsis	Male/56	None	Resolved	S/P liver transplant	Not related
024-028	Cholangitis	Male/56	Discontinued	Resolved	S/P liver transplant	Not related
024-028	Vascular pseudoaneurysm	Male/56	Discontinued	Resolved	S/P liver transplant	Not related
024-028	Complication of transplanted liver	Male/56	Discontinued	Resolved	S/P liver transplant; right hepato-jejunostomy	Not related
024-028	Portal vein stenosis	Male/56	Discontinued	Resolved	S/P liver transplant; portal vein dilatation	Not related
024-045	left inguinal hernia	Male/43	None	Resolved		Not related
024-045	Obstructive uropathy	Male/43	None	Resolved	Ureteral stone	Not related
025-005	Thyroid cancer	Male/46	None	Continuing	Radioactive iodine treatment	Not related
025-016	Chest pain	Male/53	None	Resolved	History of MI, smoking, family history of CAD	Not related
025-022	Bladder calculus	Male/26	None	Resolved		Not related
025-031	Pruritus	Female/51	Discontinued	Continuing	Also had rash; positive re-challenge	**Related**
025-033	Ureteral calculus	Male/36	None	Resolved		Not related
025-036	Malignant hepatic neoplasm	Male/56	None	Continuing	Previously enrolled in study 011	Not related
031-007	Benign prostatic hypertrophy	Male/62	None-patient had not received study drug	Resolved		Not related
031-011	Acute pancreatitis	Male/49	None	Resolved	Gallbladder polyps; MRCP revealed pancreatic divisum	**Possibly Related**
031-015	Hypomania	Female/41	None	Resolved	Secondary to antidepressant-first dose	Not related
032-002	**Toxic myopathy**	Male/44	Discontinued	Continuing	Previously enrolled in Study 007 and had elevated CK and myalgia; muscle biopsy showed necrotising (toxic) myopathy with mitochondrial myopathy	**Related**
033-001	Wrist fracture	Male/41	None	Resolved, with residual		Not related

				effects		
033-001	Wrist fracture	Male/41	None	Resolved with residual effects	Wrist surgery	Not related
035-022	Angina pectoris	Male/55	None	Resolved	Required coronary stent	Not related
035-030	Urinary tract infection	Male/71	None	Resolved	History of DM	Not related
035-030	Urosepsis	Male/71	Interrupted	Resolved		Not related
035-040	Melena	Female/36	None	Resolved		Not related
036-017	Hepatitis	Male/33	Discontinued	Resolved with residual effects	Relapse/resistant HBV	Related
036-019	Hepatitis	Male/36	Interrupted	Resolved		Not related
036-027	Contusion chest wall and shoulder sprain	Male/34	None	Resolved	Motorcycle accident	Not related
036-032	Hepatitis B	Male/48	Discontinued	Resolved	Developed hepatic encephalopathy; and required liver transplant	Not related
036-027	Hepatic neoplasm, malignant	Male/45	Discontinued	Continuing	Previously enrolled in Study 011	Not related
039-014	Facial bone fracture	Male/22	Interrupted	Resolved with residual effects	Motorcycle accident	Not related
039-021	Leptospirosis	Male/43	None	Resolved		Not related
039-026	Upper respiratory tract infection	Male/45	None	Resolved		Not related
039-031	Open wound/excoriation	Female/24	None	Resolved	Motor cycle accident	Not related
039-039	Reversible ischemic neurologic deficit	Male/50	None	Resolved, with residual effect	History of hypertension	Not related
041-022	Depression	Male/60	None	Resolved with residual effect	Suicide attempt	Not related
041-004	Bipolar disorder	Male/24	None	Resolved	History of depression	Not related
049-071	Hepatitis B/viral mutation identified	Male/39	None	Continuing	Adefovir added	Not related
055-004	Tendon injury	Male/50	None	Continuing		Not related
055-006	ALT/AST increased	Male/25	Discontinued	Resolved	Virologic breakthrough	Not related
057-	Deafness/tinnitus	Female/41	None	Resolved	History of "hum"	Unknown

008					in both ears prior to study enrollment	
057-011	Hepatitis B	Male/59	None	Continuing	Not started on telbivudine	Not related
066-004	Malignant hepatic neoplasm	Female/68	Interrupted	Resolved	Previously enrolled in study 007	Not related
067-011	Epiglottitis	Male/36	None	Resolved		Not related
067-020	Hematuria	Male/39	None	Resolved	May have been related to hemorrhoid injection week prior to event	Not related
067-029	Proliferative glomerulonephritis	Female/39	None	Resolved	History of hypertension; renal biopsy showed IgA nephropathy	Not related
067-040	Dental caries	Male/60	None	Resolved	Multiple extractions, low platelets and elevated PT	Not related
067-042	Cerebrovascular accident	Male/48	None	Resolved	History of DM	Not related
068-005	Depression	Female/45	None	Resolved	History of depression	Not related
068-005	Nasal operation	Female/45	None	Resolved	Sinus surgery	Not related
068-005	Lower limb fracture	Femle/47	None	Resolved		Not related
070-010	Ovarian fibroma	Femal/46	None	Resolved		Not related
070-021	Urinary calculus	Male/21	None	Continuing		Not related
070-027	Snake bite	Female/54	None	Resolved		Not related
070-009	Hepatitis	Male/29	None	Resolved	Adefovir added	Not related
071-022	Threatened abortion	Female/27	Discontinued	Resolved	Elective abortion performed 1 week after event	Not related
071-025	Induced abortion	Femal/32	None- study medication not started	Resolved	Embryo aplasia	Not related
071-036	Hepatitis B	Male/25	None	Resolved		Not related
079-004	Hepatitis	Male/45	None	Resolved		Not related
079-005	Hepatitis	Male/33	None	Resolved		Not related
080-031	Hepatitis B	Male/33	None	Resolved		Not related
087-022	Weight loss	Male/30	None	Resolved	History of DM	Not related
087-	Malignant hepatic	Male/56	None	Continuing		Not related

005	neoplasm					
087-007	Hepatitis	Male/31	None	Continuing		Unknown
093-025	ALT increased	Male/34	None	Resolved	Hepatitis B flare	Not related
096-003	Head injury	Male/24	None	Resolved		Not related
103-002	Hepatitis B	Female/35	None- not on study medication	Resolved		Not related
103-003	Hepatitis	Male/46	None- study medication previously discontinued	Resolved		Not related
103-014	Hepatitis	Male/32	Discontinued	Resolved	Pegylated interferon started	Not related
106-012	Ankle fracture	Male/22	None	Continuing		Not related
113-027	Malignant hepatic neoplasm	Male/32	None	Continuing	Previously enrolled in study 015	Not related
116-001	Colonic cancer	Male/61	None	Resolved		Not related
117-012	Hepatitis B	Male/39	None	Resolved		Not related
118-005	Hepatitis B	Male/35	None	Resolved	At 4 month follow-up off telbivudine	Not related
119-015	ALT increased	Male/47	None	Resolved	Adefovir added	Not related
120-010	Abortion	Female/20	None	Resolved	Elective	Not related
121-005	Aplasia, pure red cell	Male/37	None	Resolved	Attributed by investigator to hepatitis-induced suppression of hematopoiesis; confounded by duodenal ulcer	Not related
122-002	NIDDM	Male/54	None	Resolved	Not receiving LdT at time of event; diabetic at baseline	Not related
122-002	Gastric cancer	Male/54	None	Continuing		Not related
124-002	Malignancy, hepatic neoplasm	Male/54	None	Resolved	Previously enrolled in Study 011	Not related
125-001	Hyperglycemia/altered stated of consciousness	Male/59	Interrupted	Resolved	Diabetic at baseline; discontinued insulin for 1 day	Not related
126-001	Hepatic neoplasm, malignant	Male/57	None	Resolved	Previously enrolled in Study 011	Not related
129-014	Hepatic cirrhosis, partial nephrectomy (RCCA), partial hepatectomy (HCC),	Male/59	None	Continuing	Previously enrolled in study 019	Not related

133-001	Lymphoma	Male/63	None	Continuing	Previously enrolled in study 019; prior history of NHL and relapsed	Not related
134-001	Inguinal hernia	Male/61	None	Resolved		Not related

NHL= non-Hodgkin's lymphoma; RCCA= renal cell carcinoma; NIDDM= non-insulin-dependent diabetes mellitus

Medical Officer Comments: *Study 022 is ongoing, and in this submission, no tabulations of the serious adverse events were provided, only narrative summaries. From review of these narratives hepatocellular carcinoma was a relatively common SAE, but this would not be unexpected in patient population with decompensated liver disease due to HBV, or in patients who have failed antiviral therapy. Some of these cases are also reviewed as postmarketing adverse events or were reported in the 120-Day Safety Update (Section 7.7). In this study there were also a significant number of patients with hepatitis flares, some in patients on-treatment with telbivudine, and some in patients who had not started the drug or who relapsed after discontinuation. Three adverse events, one of which was considered unrelated to telbivudine by the investigator, were likely related to telbivudine based on the known safety profile for this product myopathy, toxic myopathy, and myopathy/myositis. Another adverse event of concern was deafness in patient 014-022. This patient was apparently receiving concomitant pegylated interferon, and this combination has recently been associated with an increased risk for peripheral neuropathy compared to telbivudine alone. Whether this combination could also affect other nerves such as cranial nerves is not clear at this time. A number of these serious adverse events were malignant hepatic neoplasms. Many of these were in patients who had rolled over from Study 011, in which patients with decompensated liver disease and hepatitis B were enrolled. Hepatoma is a known complication of long-standing untreated hepatitis B, and in some of these cases, HBV was suppressed; however, this adverse event is more likely related to the underlying progression of hepatitis B rather than to telbivudine. Additionally, a number of other cancers were listed as serious adverse events in this study. Because the majority of patients with these diagnoses were over the age of 50, and because the study is relatively long-term (2-years), the occurrence of such events is not entirely unexpected. However, the actual incidence of these events should be compared to the incidence in the general population. .*

Serious Adverse Events in Study NV-02C-004: See Section 7.7 for review of serious adverse events from this study provided in 120-Day Safety Update.

Serious Adverse Events in Study NV-02B-019: See Section 7.7 for review of serious adverse events from this study provided in 120-Day Safety Update.

7.3.3 Dropouts and/or Discontinuations

See Section 5.3 Individual Studies for analysis of dropouts and/or discontinuations in Studies 007 and 015. In the pooled major safety population, 12.8% lamivudine recipients and 7.9% telbivudine recipients discontinued from the study for the reasons summarized in the following table.

Table 99. Patient Disposition (Major Safety Population)

Table 2-10 Patient disposition – pooled NV-02B-007/NV-02B-015

	Lamivudine (n=852)		Telbivudine (n=847)	
	n	(%)	n	(%)
Patients discontinued from study	109	(12.8)	67	(7.9)
Reason for study discontinuation				
Adverse event	13	(1.5)	7	(0.8)
Clinical disease progression	4	(0.5)	0	
Death	2	(0.2)	1	(0.1)
Lack of efficacy after Week 24	18	(2.1)	6	(0.7)
Non-compliance	8	(0.9)	10	(1.2)
Pregnancy	6	(0.7)	5	(0.6)
Patient, investigator, or sponsor request	58	(6.8)	38	(4.5)

Source: Table 2-10 Summary of Clinical Safety

Medical Officer Comments: *In the pooled analysis, more patients in the lamivudine than telbivudine group discontinued the studies due to adverse events, clinical disease progression, for lack of efficacy after week 24, or by request of the patient, investigator or sponsor.*

Adverse Events Resulting in Treatment Discontinuation or Interruption

The most common adverse event resulting in treatment discontinuation in both treatment groups was hepatitis B exacerbation reported in 2/852 (0.2%) telbivudine- and in 8/852 (0.9%) lamivudine-treated patients. Adverse events resulting in discontinuation are summarized in the following table with respect to treatment group, AE severity (toxicity Grade), and whether an event was considered serious.

Table 100. Patients with Adverse Events Resulting in Discontinuation in Pooled Major Safety Population

Adverse Event Preferred Term	Lamivudine N= 852 n	Serious	Toxicity Grade n	Telbivudine N=849 n	Serious	Toxicity Grade
Hepatitis B	8	5	Grade 1: 1 Grade 2: 1 Grade 3: 3 Grade 4: 3	2	1	Grade 1: 1 Grade 3: 1
Vomiting	1	0	Grade 2: 1			
Mucous membrane disorder (dehydration)	1	0	Grade 2: 1			
Hepatic failure	1	1	Grade 4: 1	1	1	Grade 3: 1
ALT increased	1	1	Grade 2: 1			
Blood CK	1	0	Grade 4: 1	1	0	Grade 2: 1

increased						
Hepatic encephalopathy	1	1	Grade 4: 1			
Urticaria	1	1	Grade 2: 1			
Multiple Myeloma	1	1	Grade 4: 1			
Abdominal Distension	0			1	0	Grade 1: 1
Cardiac Failure, Congestive	0	--	--	1	1	Grade 2: 1
Fatigue	0	--	--	1	0	Grade 1: 1
Loose stools	0	--	--	1	0	Grade 1:1
Murder	0	--	--	1	1	Grade 4:1
Myopathy	0	--	--	1	0	Grade 2: 1
Nausea	0	--	--	1	0	Grade 1: 2 events
Pain in Extremity	0	--	--	1	0	Grade 1:1
Total	16 (1.9%)	10	Grade 1: 1 Grade 2: 5 Grade 3: 3 Grade 4: 7	13 (1.5%)	4	Grade 1: 7 Grade 2: 3 Grade 3: 2 Grade 4: 1

n= number of patients with AE
Source: SRAS A_AE dataset

Medical Officer Comments: *The pattern of adverse events resulting in treatment discontinuation differed between the two treatment groups. Hepatitis B exacerbation was the most common reason for treatment discontinuation in both groups, 8 patients in the lamivudine treatment arm, and 2 patients in the telbivudine arm discontinued therapy for that reason. Additionally in the lamivudine group, other adverse events which may have resulted from hepatitis B exacerbation, including hepatic failure, hepatic encephalopathy, increased ALT were numerically more common in the lamivudine group (3 patients) than the telbivudine group (1 patient). One patient in each treatment group discontinued treatment due to elevated CK; while one patient in the telbivudine group discontinued for myopathy, compared to none in the lamivudine group.*

Adverse Events Resulting in Treatment Interruption
A total of 22/849 (2.6%) telbivudine recipients and 17/852 (2.0%) lamivudine recipients had at least one treatment interruption due to an adverse events. These adverse events are summarized in the following table.

Table 101. Patients with Adverse Events Resulting in Treatment Interruption in Pooled Major Safety Population

Adverse Event Preferred Term	Lamivudine N= 852 n=events	Serious	Toxicity Grade	Telbivudine N=849 n=events	Serious	Toxicity Grade
Patients with AEs resulting in treatment interruption	17 (2.0%)			22 (2.6%)		
Blood CK increased				6	1	Grade 1: 2 Grade 2: 2 Grade 4: 2
Nausea				2	0	Grade 1: 2
Fatigue				2	0	Grade 2: 2
Diarrhea	1	0	Grade 2:1	4	0	Grade 1: 1 Grade 2:1 Grade 3:1
Myopathy				1	1	Grade 2: 1
Myalgia				2	0	Grade 1: 1 Grade 2: 1
Hepatitis B				1	0	Grade 1: 1
URI				1	0	Grade 2: 1
Pituitary tumor				2	1	Grade 2:1
Pain in extremity				1	0	Grade 1:1
Nasopharyngitis				1	0	Grade 1:1
Hepatic pain	1	0	Grade 1: 1	1	0	Grade 2:1
Gastroenteritis				1	0	Grade 2: 1
Gastritis				1	0	Grade 1:1
Gastric varices hemorrhage				1	1	Grade 4:1
Dyspnea				1	0	Grade 1:1
Dyspepsia	2	0	Grade 1:2			
Dizziness	1	1	Grade 3:1	1	0	Grade 1:1
Blood potassium decreased				1	0	Grade 2:1
Blood CK –MB increased				2	0	Grade 1: 1
Asthenia				1	0	Grade 1:1
Anosmia				1	0	Grade 1:1
Amenorrhea				1	0	Grade 1: 1
ALT increased				1	0	Grade 2: 1
Abdominal tenderness				1	0	Grade 1: 1
Abdominal pain	1	0	Grade 1: 1	1	0	Grade 3: 1
Appendicitis	1	1	Grade 4:1	0		
Head injury	1	1	Grade 2: 1			
Headache	1	0	Grade 1: 1			
Helicobacter infection	1	0	Grade 1: 1			
Hepatic neoplasm, malignant	2	2	Grade 3: 2			

Hyperlipidemia	1	0	Grade 1: 1			
Influenza	1	0	Grade 1:1			
Iodine allergy	1	0	Grade 1: 1			
Lymphadenitis	1	1	Grade 3:1			
Malaise	1	1	Grade 3:1			
Bacterial pneumonia	1	0	Grade 1: 1			
Pyrexia	1	0	Grade 1:1			
Soft tissue injury	1	0	Grade 2: 1			
Tonsillitis	1	0	Grade 2: 1			
Tooth infection	1	0	Grade 1: 1			
Viral URI	1	0	Grade 2: 1			
Vomiting	2	0	Grade 1: 1 Grade 2: 1			
Total	25	7	Grade 1: 13 Grade 2: 6 Grade 3: 5 Grade 4: 1	37	4	Grade 1: 18 Grade 2: 14 Grade 3: 2 Grade 4: 2

URI= upper respiratory infection
Source: SRAS_AE dataset

Medical Officer Comments: *Again, the pattern of adverse events resulting in treatment interruption differs between the two treatment groups. In the lamivudine treatment arm, the most common events resulting in treatment interruption were dyspepsia, vomiting, and malignant hepatic neoplasm (2 events each); while in the telbivudine arm, the most common events leading to treatment interruption were increased blood CK (6), diarrhea (4), nausea (2), myalgia (2), and fatigue (2).*

7.3.4 Significant Adverse Events

CK Elevation

In the applicant's pooled analysis (studies 007 and 015), the incidence of new-onset CK elevation (Grade 1/2 or 3/4) was higher in telbivudine than lamivudine-treated patients in the first and second year of the study. In lamivudine patients, the proportion of patients with CK elevation declined slightly from the first to second year; while in telbivudine patients, the incidence was similar in both years of the study, as shown in the following table.

Table 102. New Onset CK Elevations in Major Safety Population

Table 5-8 New-onset Grade 1/2 and Grade 3/4 CK elevations – Pooled NV-02B-007/NV-02B-015

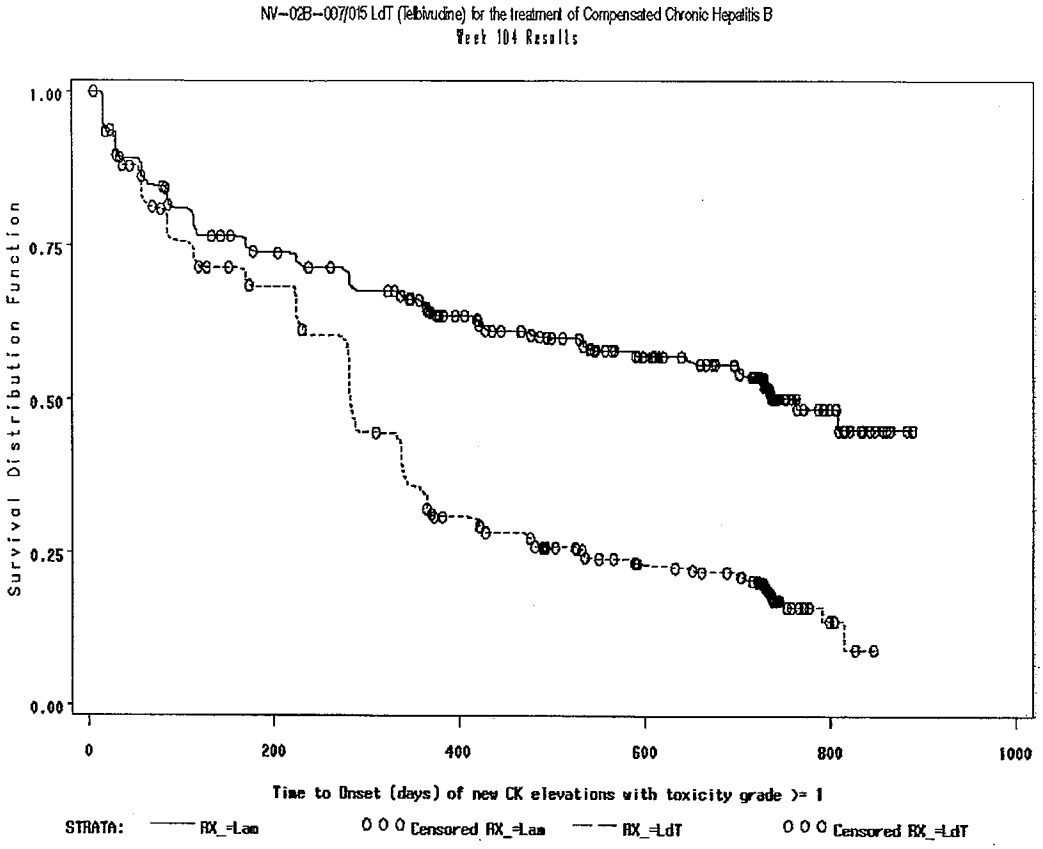
	Grade 1/2				Grade 3/4			
	Lamivudine (N=852)		Telbivudine (N=847)		Lamivudine (N=852)		Telbivudine (N=847)	
Laboratory Test	n	(%)	n	(%)	n	(%)	n	(%)
Baseline to Week 52								
Creatine kinase (CK)	281	(33.0)	514	(60.7)	26	(3.1)	65	(7.7)
Post Week 52 to End of Study								
Creatine kinase (CK)	234	(27.5)	517	(61.0)	10	(1.2)	63	(7.4)
All Visits								
Creatine kinase (CK)	365	(42.8)	566	(66.8)	34	(4.0)	107	(12.6)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.1.1 and Table 14.3.1.4.1.2]

Time to onset of new CK elevation

In the statistical reviewer's analysis, 673/850 (79%) telbivudine patients, and 399/852 (47%) lamivudine patients had new CK elevations with toxicity ≥ 1 ($p<0.001$ using Fisher's exact test). Additionally, the occurrence of new-onset CK elevation (Grade 1-4) was more rapid in the telbivudine than the lamivudine group over the period of the study (treatment period was up to 104 weeks, 728 days, with 4 month follow-up period), as shown in the following figure. The median time to new CK elevation was 282 days in the telbivudine group compared to 764 days in the lamivudine group ($p<0.001$ using the log rank test).

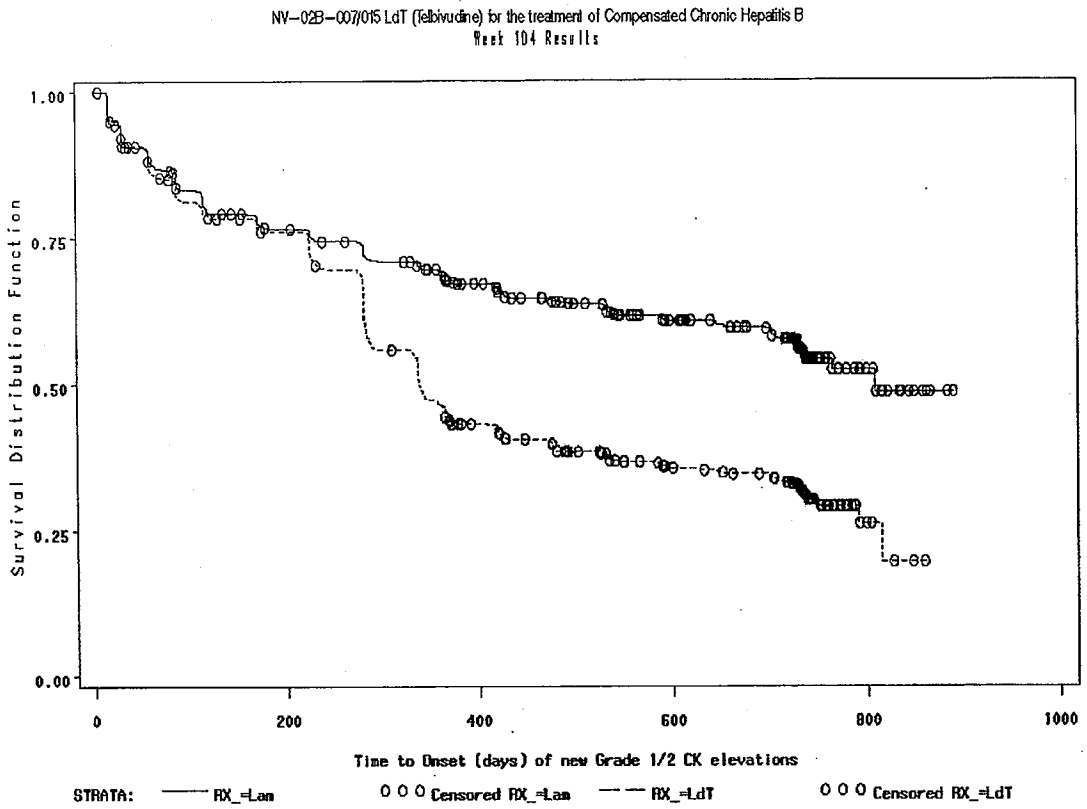
Figure 10. Time to onset of new-onset CK elevation (> Grade 1) in Major Safety Population



Medical Officer Comments: *The rate of new onset CK elevation was similar in the two groups up to about Day 100. At that point, there was clear divergence in rates between the treatment groups. There appear to be only a few data points for the telbivudine group between Days 200 and 300.*

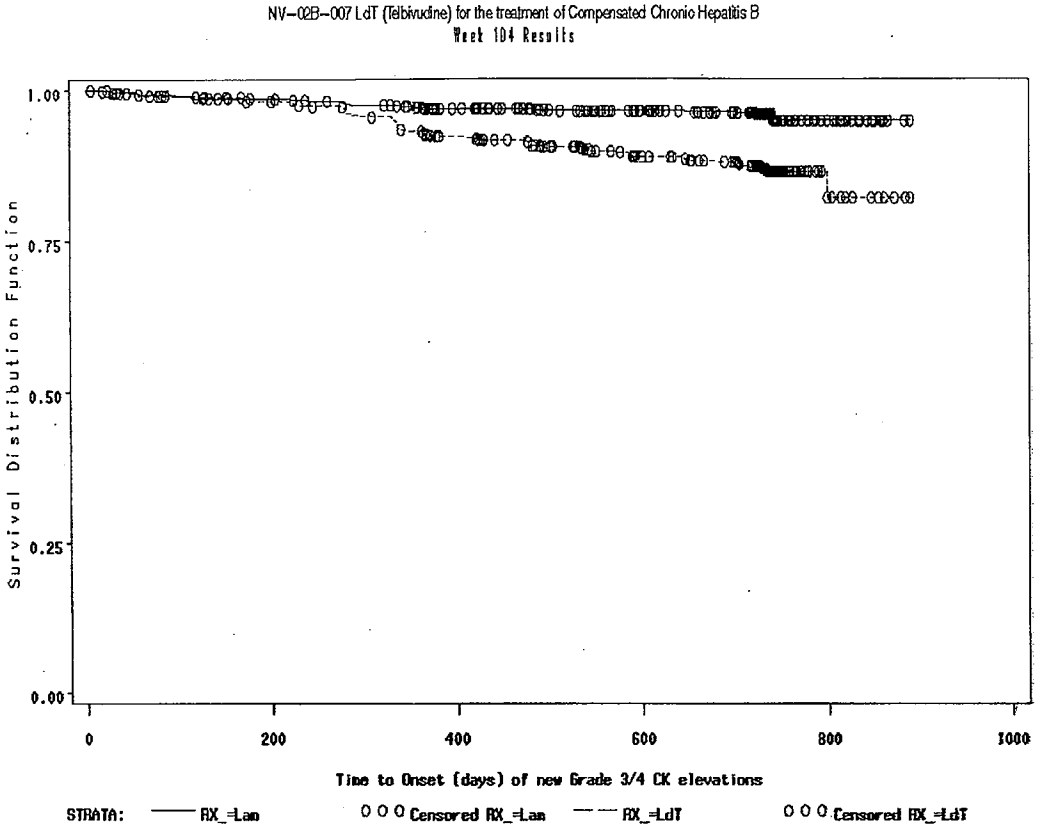
In the statistical analysis conducted by Dr. Fraser Smith, the percentage of patients with new onset Grade 1 or 2 CK (worst toxicity) was 566/850 (67%) in the telbivudine group and 365/852 (43%) in the lamivudine group ($p<0.001$ using Fisher's exact test). A Kaplan-Meier plot of time to onset of Grade 1 or 2 CK elevations shows a significantly earlier onset in telbivudine (median time 338 days) than lamivudine patients (median time 808 days) as depicted in the following figure ($p< 0.001$ using the log rank test).

Figure 11. Time to New-Onset CK Elevation (Grade 1/2) in Major Safety Population



The proportion of patients with new Grade 3 or 4 CK elevation was significantly higher in telbivudine patients (107/850, 13%) compared to 34/852 (4%) in lamivudine patients in Dr. Fraser Smith's analysis ($p<0.001$ using Fisher's exact test). Similarly, the time to onset of Grade 3 or 4 CK elevation was more rapid in telbivudine than lamivudine-treated patients, as shown in the following Kaplan-Meier analysis ($p< 0.001$ using log rank test).

Figure 12. Time to New-Onset CK Elevation (Grade 3/4) in Major Safety Population



New onset by baseline toxicity

In the applicant's analysis, the majority of patients had a baseline CK toxicity Grade 0 or 1 in each of the treatment groups. Among patients with baseline CK Grade 0 toxicity, a higher proportion developed Grade 2 CK toxicity in the telbivudine than in the lamivudine group (22.7% vs. 4.7%). Among those with baseline CK toxicity Grade 1, 5.4% in the telbivudine group and 3.2% in the lamivudine group developed Grade 2 CK elevation; and 1.1% and 0.5% developed Grade 3 CK elevation respectively. This analysis is shown in the following table.

Table 103. Maximal On-Treatment CK Toxicity by Baseline CK Toxicity in Major Safety Population

Table 5-9 Baseline CK toxicity grade vs. maximal on-treatment CK toxicity grade – Pooled NV-02B-007/NV-02B-015

	Worst on-treatment toxicity grade											
	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Total	
Baseline grade[1]	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Telbivudine (N=847)												
Grade 0	139	(16.4)	328	(38.7)	192	(22.7)	36	(4.3)	44	(5.2)	739	(87.2)
Grade 1	4	(0.5)	26	(3.1)	46	(5.4)	9	(1.1)	14	(1.7)	99	(11.7)
Grade 2	0		0		3	(0.4)	0		4	(0.5)	7	(0.8)
Grade 3	0		1	(0.1)	0		0		0		1	(0.1)
Grade 4	0		1	(0.1)	0		0		0		1	(0.1)
Total	143	(16.9)	356	(42.0)	241	(28.5)	45	(5.3)	62	(7.3)	847	(100.0)
Lamivudine (N=852)												
Grade 0	389	(45.7)	298	(35.0)	40	(4.7)	5	(0.6)	17	(2.0)	749	(87.9)
Grade 1	5	(0.6)	52	(6.1)	27	(3.2)	4	(0.5)	3	(0.4)	91	(10.7)
Grade 2	1	(0.1)	4	(0.5)	1	(0.1)	1	(0.1)	4	(0.5)	11	(1.3)
Grade 3	0		0		0		0		0		0	
Grade 4	0		0		0		0		1	(0.1)	1	(0.1)
Total	395	(46.4)	354	(41.5)	68	(8.0)	10	(1.2)	25	(2.9)	852	(100.0)

[1] Screening value used if Baseline unavailable.
Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.18.2]

Medical Officer Comments: *For patients with baseline CK of 0 or 1, a higher proportion of telbivudine-treated patients developed CK elevations of Grade 2, 3 or 4 in the telbivudine than the lamivudine group. Too few patients had baseline CK elevations of Grade 2 and higher to draw any meaningful comparison.*

Resolution of Grade 3 or 4 CK elevation

In the applicant's analysis of the pooled safety database, the majority of Grade 3 or 4 CK elevations resolved to Grade 1 or 2. As shown in the following table, more CK elevations resolved to normal value or pre-treatment value in the lamivudine than in the telbivudine group; and more in the telbivudine group remained Grade 3 or 4 at the next visit (CK retested at scheduled or unscheduled visit), or at the last visit.

Table 104. Resolution of New-Onset CK Elevations (Grade 3/4) in Major Safety Population

Table 5-10 Resolution of on-treatment, new-onset Grade 3/4 CK elevations – Pooled NV-02B-007/NV-02B-015

New onset of Grade 3/4 CK	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)
Number of patients	34 (4.0)	107 (12.6)
Number of episodes	38	153
Remain Grade 3/4 at next visit	2 (5.3)	16 (10.5)
Resolved to normal value	13 (34.2)	26 (17.0)
Resolved to pre-treatment value	5 (13.2)	11 (7.2)
Resolved to Grade 1/2	16 (42.1)	89 (58.2)
Episode at last visit	2 (5.3)	11 (7.2)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.18.4]

As a corollary, the applicant also analyzed duration of Grade 3 or 4 CK elevations. The following table shows that most Grade 3 or 4 CK elevations lasted only one visit in both treatment groups; but lasted for 2 or more consecutive study visits in more telbivudine than lamivudine-treated patients.

Table 105. Duration of New-Onset CK Elevation (Grade 3/4) in Major Safety Population

Table 5-12 Duration of on-treatment, new-onset Grade 3/4 CK by number of consecutive visits – Pooled NV-02B-007/NV-02B-015

	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)
Number of patients with new-onset Grade 3/4 CK	34 (4.0)	107 (12.6)
Total number of Grade 3/4 episodes lasting:	38 (100.0)	153 (100.0)
Episodes lasting 1 visit	36 (94.7)	137 (89.5)
Episodes lasting 2 visits	1 (2.6)	12 (7.8)
Episodes lasting 3 visits	1 (2.6)	3 (2.0)
Episodes lasting 4 visits	0	1 (0.7)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 3.4.18.5]

Medical Officer Comments: *A total of 16/153 (10.5%) Grade 3/4 CK episodes lasted more than 1 study visit in the telbivudine group compared to 2/38 (5.3%) in the lamivudine group. This analysis, however, does not address whether treatment was interrupted or discontinued for CK elevation for any of these patients.*

Recurrence of CK elevation

Patients treated with telbivudine were more likely to have recurrent Grade 3/4 CK elevations than those treated with lamivudine as shown in the following table.

Table 106. Recurrence of CK Elevation (Grade 3/4) in Major Safety Population

Table 5-11 Recurrence of on-treatment Grade 3/4 CK – Pooled NV-02B-007/NV-02B-105

007/015	Lamivudine (N=852) n (%)	Telbivudine (N=847) n (%)
Number of patients with new-onset Grade 3/4 CK	34 (4.0)	107 (12.6)
With 1 Grade 3/4 episode	30 (88.2)	75 (70.1)
With 2 Grade 3/4 episodes	4 (11.8)	21 (19.6)
With 3 Grade 3/4 episodes	0	8 (7.5)
With 4 Grade 3/4 episodes	0	3 (2.8)

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.18.5]

Myopathy/Myositis

The overall incidence of adverse events in the musculoskeletal/connective tissue disorder SOC was similar in the lamivudine (115/687, 16.7%) and telbivudine (119/680, 17.5%) treatment groups in Study 007. Two cases of myositis and two cases of myopathy in telbivudine-treated patients and one case of myositis in lamivudine-treated patients were reported in that study. In Study 015, polymyositis was reported in one telbivudine-treated patient. No adverse events of rhabdomyolysis were reported in these studies. The cases of myopathy and myositis are summarized in the following table.

Table 107. Myopathy and Myositis in Major Safety Population

Table 4-15 Occurrence of myopathy and myositis – major safety population

Site-patient ID	Event (verbatim)	Event (preferred term)	SAE	Toxicity Grade	Relationship to study drug	Action with study drug	Outcome
Lamivudine							
007-008-026	Myositis (worsening)	Myositis	No	Grade 1	Not reasonably or possibly related	None	Resolved, no residual effects
Telbivudine							
007-012-001	Drug-induced myopathy	Myopathy	Yes	Grade 2	Reasonably or possibly related	Interrupted	Resolved, no residual effects
007-054-031	Myopathy	Myopathy	No	Grade 2	Reasonably or possibly related	Discontinued	Resolved, no residual effects
015-010-023	Polymyositis	Polymyositis	Yes	Grade 3	Not reasonably or possibly related	None	Resolved, no residual effects
007-008-019	Right upper arm pain	Myositis	No	Grade 1	Not reasonably or possibly related	None	Resolved, no residual effects
007-057-123	Muscle weakness and tenderness	Myositis	No	Grade 1	Not reasonably or possibly related	None	Resolved, no residual effects

Source: [NV-02B-007 Wk 104 – Listing 16.2.7.1] and [NV-02B-015 Wk 104 – Listing 16.2.7.1]

***Medical Officer Comments**: The adverse events of myopathy, myositis and polymyositis were confirmed in the SRAS A_AE dataset. Only one of these events was considered serious, polymyositis in patient number 015-010-023, and all events reportedly resolved. In both cases of myopathy, telbivudine was discontinued or interrupted.*

The applicant provided a brief narrative for each of these cases, and this reviewer agrees with the investigator's attribution of the events to study medication for patients 007-012-001 and 007-054-031 (drug-related events in both cases); but disagrees with the assessment made for patients 007-057-123 and 015-010-023, in that both events could be considered at least possibly related (there was some temporal relationship, accompanying CK elevations, and positive de-challenge for 007-057-123). For the other two patients, 007-008-026 and 007-008-019, insufficient information was provided to fully assess the relationship of the adverse events to study drug. However, both events as described seem unlikely related to study medication. In the case of 007-008-026, the event resolved quickly while the patient remained on treatment (lamivudine); and in patient 007-008-019, the event was described as right arm pain (and coded as myositis), which also resolved on treatment.

The adverse event (A_AE) dataset and laboratory (ALab2) dataset were searched for additional information regarding CK elevation in the patients who experienced myopathy or myositis. As shown in the table below, there was no clear overall pattern of CK elevation in these patients, although, the patients with myositis or polymyositis in whom these events were at least possibly related to study drug, CK elevations from baseline were significant.

Table 108. CK Elevation in Patients with Adverse Events of Myopathy or Myositis in Study 007 and 015

Patient	Treatment	Adverse Event	AE Study Week/Day	Baseline CK IU/La	CK on approx. Study Day of AE (Toxicity Grade)b	Maximum CK level during study (Week/Day)
007-008-026	Lamivudine	Myositis	8/67	189	186-318 (Grade 0-1)	1710 (92/ 645)
007-012-001	Telbivudine	Myopathy*	40/300	256	538 (Grade 1)	538 (40/295)
007-054-031	Telbivudine	Myopathy	40/282	80	385 (Grade 1)	2934 (76/569)
007-008-019	Telbivudine	Myositis	2/27	203	44-179 (normal)	338 (48/344)
007-057-123	Telbivudine	Myositis*** Muscles weakness and tenderness	32/275 60/425	458	1127 (Grade 2) 2234 (Grade 4)	3890 (52/355)
015-010-023	Telbivudine	Polymyositis****	40/325 76/545	62	642 (Grade 2) 2233 (Grade 4)	2233 (76/545)

a CK ULN was 195 IU/L for these patients
b Note that Toxicity Grade was determined by taking the difference from the baseline (or screening) CK value and using DAIDS, 1992 Toxicity Table.
* Myofibrillar degeneration on muscle biopsy
*** Muscle biopsy showed evidence of myositis; this patient had a second adverse event of muscle weakness and tenderness which was not coded as myositis.
**** This patient had two separate adverse events of polymyositis. The muscle biopsy showed muscle atrophy and lysis of muscle fibers.

Medical Officer Comments: *Both adverse events of myopathy were reported at Study Week 40, and in both cases, CK elevation was reported as Grade 1. For the patients with myositis or polymyositis, which was at least possibly drug-related, (007-057-123 and 015-010-023), events were reported at Study Week 32 and 40, respectively. CK elevations at the time of the adverse events for these cases were reported as toxicity Grades 2-4; while in the cases where the events were not likely related to study drug (007-008-019 and 007-008-026), CK values recorded around the time of the event were normal, or minimally elevated.*

Applicant's analysis of musculoskeletal AEs associated with CK elevation in Study 015:

Table 109. Musculoskeletal AEs during a new-onset CK Elevation

Table 12-6 On-treatment adverse events possibly related to myopathic/muscle injury process occurring within (+/-) 30 days of a new onset of CK elevation, baseline to end of study - safety population

Preferred term	Lamivudine N = 165 n (%)	Telbivudine N = 167 n (%)	Total N = 332 n (%)
Within a new onset of grade 1/2 CK	61	135	196
Patients reporting an AE	0	12 (8.9)	12 (6.1)
Asthenia	0	0	0
Fatigue	0	9 (6.7)	9 (4.6)
Muscular weakness	0	1 (0.7)	1 (0.5)
Myalgia	0	0	0
Pain in extremity	0	1 (0.7)	1 (0.5)
Polymyositis	0	1 (0.7)	1 (0.5)
Within a new onset of grade 3/4 CK	6	19	25
Patients reporting an AE	0	3 (15.8)	3 (12.0)
Asthenia	0	1 (5.3)	1 (4.0)
Fatigue	0	1 (5.3)	1 (4.0)
Muscular weakness	0	0	0
Myalgia	0	1 (5.3)	1 (4.0)
Pain in extremity	0	1 (5.3)	1 (4.0)
Polymyositis	0	1 (5.3)	1 (4.0)
Within a new onset of grade 1/4 CK	61	136	197
Patients reporting an AE	0	14 (10.3)	14 (7.1)
Asthenia	0	1 (0.7)	1 (0.5)
Fatigue	0	10 (7.4)	10 (5.1)
Muscular weakness	0	1 (0.7)	1 (0.5)
Myalgia	0	1 (0.7)	1 (0.5)
Pain in extremity	0	2 (1.5)	2 (1.0)
Polymyositis	0	1 (0.7)	1 (0.5)

Source: Post-text table 14.3.1.3.5.9

Medical Officer Comments: *In this study, none of these adverse events were associated with CK elevation in lamivudine-treated patients; while for telbivudine, 12/135 (8.9%) of patients with a Grade 1 or 2 CK elevation, and 3/19 (15.8%) of patients with Grade 3 or 4 CK elevation experienced muscle-related adverse events.*

Association of Musculoskeletal Adverse Events and CK elevations

In the following analysis, the applicant analyzed whether adverse events which could indicate muscle injury or myopathy were associated with CK elevation (at any time) in the pooled safety database. A total of 11/34 (32.4%) lamivudine patients and 30/107 (28%) telbivudine patients with Grade 3/4 CK elevation experienced an adverse event in this category; while 50/365

(13.7%) lamivudine patients and 90/566 (15.9%) telbivudine patients with Grade 1/2 CK elevation experienced an adverse event in this category.

Table 110. Association of Musculoskeletal Adverse Events with new-onset CK Elevation

Table 4-16 Summary of on-treatment adverse events possibly related to a myopathy/muscle injury process, by occurrence of new-onset CK elevations at any time – Pooled NV-02B-007/NV-02B-015

	Lamivudine			Telbivudine		
Preferred Term	With Grade 3/4 CK (N=34) n (%)	With Grade 1/2 CK (N=365) n (%)	Without Grade 1-4 CK (N=453) n (%)	With Grade 3/4 CK (N=107) n (%)	With Grade 1/2 CK (N=566) n (%)	Without Grade 1-4 CK (N=174) n (%)
Patients reporting an adverse event	11(32.4)	50(13.7)	73(16.1)	30(28.0)	90(15.9)	36(20.7)
Asthenia	0	5(1.4)	6(1.3)	4(3.7)	8(1.4)	7(4.0)
Fatigue	7(20.6)	33(9.0)	55(12.1)	17(15.9)	65(11.5)	24(13.8)
Malaise	2(5.9)	1(0.3)	2(0.4)	1(0.9)	3(0.5)	0
Muscular weakness	0	0	1(0.2)	0	2(0.4)	0
Musculoskeletal discomfort	0	2(0.5)	0	0	2(0.4)	0
Musculoskeletal pain	0	0	2(0.4)	0	1(0.2)	0
Myalgia	3(8.8)	6(1.6)	8(1.8)	11(10.3)	13(2.3)	3(1.7)
Myopathy	0	0	0	1(0.9)	1(0.2)	0
Myositis	1(2.9)	0	0	1(0.9)	0	1(0.6)
Pain	0	2(0.5)	4(0.9)	2(1.9)	2(0.4)	3(1.7)
Pain in extremity	0	8(2.2)	4(0.9)	3(2.8)	8(1.4)	2(1.1)
Polymyositis	0	0	0	1(0.9)	0	0

Source: [SRAS – NV-02B-007/NV-02B-015 Table 14.3.1.4.18.1]

Medical Officer Comments: *This analysis is limited by the fact that the CK values were not necessarily temporally related to the adverse event. For example, for the 34 patients with a Grade 3/4 CK in the lamivudine group, muscle-related adverse events may have occurred before, after, or at the same time as the CK elevation. A higher proportion of patients who reported one of these adverse events had no CK elevation than had Grade 1/2 CK elevation in both treatment groups; whereas the proportion of patients with an adverse event who also developed Grade 3/4 CK elevation was higher than the proportion with no CK elevation or Grade 1/2 elevation in both groups. Whether fatigue and malaise should be classified as a myopathy/muscle injury event is debatable, but certainly fatigue was associated with CK elevation. The term, asthenia, refers to weakness and/or loss of strength and is appropriately included in this analysis. For the preferred term, pain, used in the table above, the applicant searched the SOC General Disorders and Administration Site conditions. The events described under the preferred term, pain, included aches, generalized aches, body aches, which likely could have been coded as myalgias, and should thus be included in this analysis.*

A more meaningful analysis by the applicant was relationship between muscle-related adverse events occurring within 30 days of a new onset CK elevation. Overall, 65/673 (9.7%) telbivudine patients with any CK elevation (Grades 1-4) experienced a muscle-related adverse event within 30 days of that elevation in comparison to 19/399 (4.8%) lamivudine patients with any CK elevation. Higher proportions of telbivudine than lamivudine treated patients developed muscle-related adverse events within a 30 day window of a CK elevation whether it was Grade 1 or 2 or Grades 3 or 4 as shown in the following table.