CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-154

MEDICAL REVIEW(S)

MEMORANDUM

Medical Officer's Review of Complete Response

NDAs:	22-154 Tyzeka (telbivudine) 2-011 SLR-002 Tyzeka (telbivudine)
Date of Original Submission (NDA 22-154):	December 21, 2007
Date of Submission of Complete Response: **Date of Submission of NDA 22-011 SLR-002:**	February 27, 2009 April 28, 2009
Date of Review:	April 27, 2009
Applicant:	Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, NJ 07936-1080
Formulation:	Oral solution 100 mg/5 mL
Indication:	Treatment of Chronic Hepatitis B
Reviewer:	Mary Singer, MD, Ph.D. Medical Officer, DAVP

Background

NDA 22-154 was originally submitted on December 21, 2007, and was reviewed in conjunction with the simultaneous submission, NDA 22-011 S-001, an efficacy supplement which contained safety, efficacy, and resistance data for 2 years of telbivudine treatment in subjects with chronic hepatitis B. NDA 22-011 S-001 was approved on January 23, 2009. At that time, because of new safety information regarding the development of peripheral neuropathy, particularly when telbivudine is given in combination with alfa interferons, the patient package insert was converted to a Medication Guide and a Risk Evaluation and Mitigation Strategy (REMS) was submitted by the applicant. The REMS consisted of the Medication Guide and a timetable for assessment of the Medication Guide. The REMS was approved and the Medication Guide was included with patient labeling.

NDA 22-001 SLR-002 was submitted on April 28, 2009 because the prescribing information for Tyzeka tablets and oral solution are included in the same label. This supplemental labeling revision includes a cross-reference to NDA 22-154, and includes all Tyzeka prescribing information, including the package insert and Medication Guide with Patient Instructions for use, supporting the new oral solution dosage form, Tyzeka oral solution.

A Complete Response for NDA 22-154 was issued on October 21, 2008, based on the deficiencies noted below. Included in the original NDA 22-154 submission were Chemistry, Manufacturing and Controls (CMC) data, Clinical Pharmacology data for telbivudine dosing for patients with renal impairment, as well as data from a drug-drug interaction (telbivudine-tenofovir DF) study. NDA-22-154 contained no safety and efficacy information, but cross-referenced the safety and efficacy data in NDA 22-011 S-001. The clinical pharmacology and clinical safety data from the telbivudine-tenofovir DF interaction study were reviewed in conjunction with NDA 22-011 S-001, and information from the latter study was included in the drug interactions section of the Tyzeka package insert approved January 23, 2009. Tyzeka oral solution was previously determined to be bioequivalent to the Tyzeka tablet formulation in a study submitted with the original NDA 22-011.

A Complete Response for NDA 22-154 was issued because of the following deficiencies:

1. [redacted] b(4)

2. [redacted] b(4)

b(4)

3

b(4)

4. Please submit revised carton and/or container labels as follows:
Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling (21 CFR 314.50(1)(1)(i)J in structured product labeling (SPL) format as described at http://ww.fda.gov/oc/datacouncillspl.html.

6. You must submit a proposed REMS, as described below:

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS (not reproduced here since these requirements are identical to those required under Tyzeka Tablet NDA 22-011).

The applicant's Complete Response submitted on February 27, 2009, contains the following information, as summarized below:

1.

2. b(4)

3. b(4)

4. Revised Tyzeka carton and container labels including the statement, "PHARMACIST: Dispense with enclosed Medication Guide" were included.

5. Revised proposed labeling for Tyzeka oral solution, including a revised package insert and Medication Guide with Instructions for Patient Use, as well as the labeling in SPL format, were submitted.

6. A draft Risk Evaluation and Mitigation Strategy (REMS), incorporating NDA number 22,154 into the approved REMS for the Tyzeka tablet for NDA 22-011 S-001 was included.

Additionally, the submission included quality information for the new formulation, Tyzeka oral solution, including the full description and composition of the drug product, pharmaceutical development, manufacture and control, stability, and container closure system. This CMC information was reviewed by Dr. Andrew Yu, and was considered acceptable.

For this review, consultations were obtained from Office of Safety and Epidemiology (OSE) Divisions of Risk Management (DRISK) for evaluation of the proposed Medication Guide and REMS, and the Division of Medication Error Prevention and Analysis (DMEPA) for evaluation of the proposed product labeling related to dosing of Tyzeka oral solution.

DAVP also requested additional information from the applicant regarding their pediatric development plan, as required with any new drug formulation under PREA regulations. The applicant's pediatric development plan was officially submitted to the NDA on April 8, 2009. The proposed pediatric investigational plan and other information applicable to PREA were subsequently presented to the CDER Office of New Drugs Pediatric Review Committee on April 8, 2009.

Review of NDA Complete Response and NDA 22-011 SLR-002:

Chemistry, Manufacturing and Controls (CMC)/Devices

Tyzeka oral solution contains 20 mg/mL telbivudine. The standard dose of Tyzeka in patients without renal impairment is 600 mg daily as the tablet formulation or as 30 mL (600 mg) Tyzeka oral solution. Dose adjustment is required for patients with renal impairment, as discussed in the following section. As proposed [redacted] were to be provided with the oral solution. This is a revision from the original NDA in which only the 30 mL dosing cup was provided with the oral solution, and was submitted in response to the CR letter, in which DAVP requested that the applicant [redacted] From a CMC viewpoint, the proposed [redacted], and the CDER Office of Compliance has determined

b(4)

b(4)

that all manufacturing facilities are adequate. Please see Dr. Andrew Yu's CMC review of April 15, 2009 for further details.

Medical Officer Comments: *DMEPA reviewers considered the use of* [redacted] b(4)

[redacted]

[redacted] *This reviewer agrees that the* [redacted]
proposed, are unacceptable for [redacted] b(4)
DMEPA reviewers also recommended a labeling comprehension (or actual use study) to evaluate the [redacted] *as proposed or* [redacted]

[redacted]

Proposed Dosing for Patients with Renal Impairment
Proposed dosing regimens for Tyzeka oral solution in patients with normal creatinine clearance and in those with renal impairment are shown in the table below in comparison to the approved dosing regimens for the Tyzeka 600 mg tablet.

Table 1. Proposed Dosing for Tyzeka Oral Solution and Tablets based on Creatinine Clearance

Creatinine Clearance (mL/min)	Oral Solution (100 mg/5 mL)	Tablet (600 mg)
≥ 50	30 mL (600 mg) once daily	1 tab every 24 hours
30-49	20 mL (400 mg) once daily	1 tab every 48 hours
< 30 (not requiring dialysis)	10 mL (200 mg) once daily	1 tab every 72 hours
ESRD	[redacted]	1 tab every 96 hours

b(4)

In her Clinical Pharmacology review for NDA 22,154 of October 15, 2008, Dr. Jenny Zheng found the newly proposed doses of Tyzeka oral solution for patients with renal impairment acceptable except for the dose proposed for patients with ESRD requiring dialysis. See deficiency number 2 above which was included in the Complete Response letter.

[redacted] b(4)

[redacted]

In a teleconference with the applicant on April 8, 2009, the Clinical Pharmacology reviewer, Dr. Jenny Zheng and Deputy Director, Dr. Kellie Reynolds discussed with the applicant the issue of [redacted] b(4)

[redacted] Specific comments and requests for additional clinical pharmacology information were sent to the applicant on April 9, 2009.

b(4)

b(4)

Medical Officer Comments: [redacted]

b(4)

Proposed Package Insert Revisions

The applicant's revisions to the approved Tyzeka package insert include changes to the Highlights section to describe the dosing of Tyzeka oral solution in patients with renal impairment, and to the Full Prescribing Information which includes changes to Section 2, Dosage and Administration, Section 3, Dosage Forms and Strengths, Section 11, Description, Section 16, How Supplied/Storage and Handling, and section 17, Patient Counseling Information. No new safety information was included in the proposed labeling; nor was any new clinical information, other than the new dosing recommendations for Tyzeka oral solution.

Medical Officer Comments: *The proposed changes to the package insert are acceptable*

b(4)

[redacted] *A number of minor revisions to the applicant's proposed changes will also be discussed with the applicant.*

Several minor revisions to the package insert were also made by the applicant, as follows. In section 2, Dosage and Administration, the following statement was added:

[redacted] may be considered for patients who have difficulty with swallowing tablets." b(4)

Medical Officer Comments: *The addition of this statement is acceptable.*

In section 17, Patient Counseling Information, the following statement was added:

"Patients on a ——— sodium diet should be advised that Tyzeka oral solution contains approximately 47 mg of sodium per 600 mg dose (30 mL)." b(4)

Medical Officer Comments: The term ——— sodium diet may be confusing and should be changed to "low" sodium diet.

Additional DMEPA labeling comments relayed to the applicant on April 14, 2009 were as follows:

All Labels and Labeling:

1. Increase the prominence of the established name such that it is commensurate with the prominence of the trade name taking into account all pertinent factors including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

2. Revise the statement of strength to read "100 mg/5 mL" which may minimize the potential for medication errors due to miscalculations and is consistent with the expression of strength for most oral solutions.

Package Insert Labeling:

3. Revise to include a statement prior to Table 1 to emphasize that the regimen for the oral solution is different from the tablets.

4. We note th ——— b(4)
——— Revise to include the frequency (i.e., once daily) for all oral solution doses in this table.

Medical Officer Comments ———

b(4)

Proposed Medication Guide and REMS

The proposed REMS includes a Medication Guide and timetable for submission of assessments. The proposed REMS is unchanged from the REMS approved for Tyzeka tablets, NDA-22-011 S-001 on January 23, 2009, except for the addition of NDA-22-154. The timetable for submission of assessments is unchanged and will follow the schedule approved for the REMS approved for Tyzeka tablets.

The Division of Risk Management (DRSIK) in the Office of Surveillance and Epidemiology (OSE) was consulted to evaluate the proposed package insert, Medication

Guide and Patient Instructions for use, as well as the proposed REMS. DRISK reviewers found the applicant's proposed REMS acceptable with the addition of NDA-22-154. DRISK also had the following comments for the applicant regarding the Medication Guide and REMS:

1. We remind the Applicant of their requirement to comply with 21 CFR 208.24

A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

2. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:
    - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
    - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
3. The Applicant's proposed timetable for assessments (18 months, 3 years, and 7 years) is acceptable. The Applicant should submit for review a detailed plan to evaluate patients' understanding about the safe use of Tyzeka (telbivudine) at least 2 months before they plan to conduct the evaluation. The submission should include:
    - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Tyzeka (telbivudine). This should include, but not be limited to:
        - Sample size and confidence associated with that sample size
        - How the sample will be determined (selection criteria)
        - The expected number of patients to be surveyed
        - How the participants will be recruited
        - How and how often the surveys will be administered
        - Explain controls used to minimize bias
        - Explain controls used to compensate for the limitations associated with the methodology

- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

3. We recommend DAVP include in the approval letter a reminder of the Applicant's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including:
   a. An evaluation of patients' understanding of the serious risks of Tyzeka (telbivudine)
   b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
   c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

We have the following comments on the proposed Medication Guide:

4. The Patient Instructions for Use were relocated at the end of the Medication Guide. [redacted] b(4)

   The applicant should label each figure and reference the figures in the text of the Patient Instructions for Use as appropriate.

5. In the description of the supplies needed to take a dose of Tyzeka Oral Solution, the applicant should clarify what is meant by a [redacted] b(4)

6. [redacted] b(4)

7. The applicant should magnify the picture which demonstrates the patient pouring and measuring their dose of medicine, to show the dose matching up with one of the lines on the dosing cup.

Medical Officer Comments: DRISK comments regarding the proposed Medication Guide and REMS were relayed to the applicant.

Proposed Pediatric Development Plan

The applicant provided a pediatric development plan upon request of the Division, and as required by FDAAA. The applicant proposes to study telbivudine for treatment of chronic hepatitis B in children between the ages of 2 and < 18 years old. [redacted] b(4)

Tyzeka oral solution (100 mg/5 mL) or the 600 mg Tyzeka tablet formulations can be used in the pediatric patient population.

The proposed pediatric studies are shown in the following table

b(4)

Table 2. Summary of Proposed Pediatric Studies (from applicant's Pediatric Investigation Plan, submitted April 8, 2009)

Descriptor	
Clinical phase	
Study design	
Planned First Patient-in	
Age groups	
Objectives	
Number of sites	
Telbivudine (LdT) group	
Comparator group	
Tx duration/Study duration	
Planned no. of patients/group	

b(4)

b(4)

b(4)

b(4)

In the original NDA 22,154, submitted on December 21, 2007, the applicant requested a [redacted] and requested deferral of pediatric studies in children between [redacted] as requested with the original NDA 22-011, submitted December 5, 2005. At the time of approval, October 25, 2006, pediatric studies in under PREA were deferred in pediatric subjects from birth to 16 years of age. For the current NDA 22,154 studies in pediatric subjects from birth to 2 years will

b(4)

be deferred until September 30, 2016, pending a final decision regarding the risk/benefit of treatment in this age group (i.e. until after completion and review of pediatric studies in subjects 2 to < 18 years old); and will be deferred in pediatric subjects for ages 2 to 18 years until September 30, 2013, because this application is ready for approval and the pediatric data are not yet available.

Medical Officer's Comments: *The applicant's proposed pediatric development plan, the proposed PREA deferrals and post-marketing PREA commitments were presented to the CDER/OND Pediatric Review Committee on April 8, 2009, and were considered acceptable. It should be noted that an amended Pediatric Written Request for pediatric subjects between the ages of 2 through 16 years was issued July 27, 2007.*

Conclusions and Recommendation on Regulatory Action:

Approval of NDA 22.154, as amended, i.e [redacted]

b(4)

[redacted] Additionally, the dosing cup, as currently proposed may be difficult for patients to read because the demarcations for doses are not distinct, and because the cup includes extraneous markings for measurements which will not be used in dosing.

In conjunction with NDA 22-154, approval of NDA 22-011 SLR-002 is recommended because Tyzeka tablet and oral solution labeling are included in the same Tyzeka labeling.

Recommended Post-marketing Requirements:

1. **PREA Committments:**

- Deferred pediatric study/substudy for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from 2 to <18 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from 2 to < 18 years of age to support dose-selection for the efficacy and safety assessment.

    - Protocol Submission: completed
    - Study Start Date: March, 2009
    - Final Report Submission: September, 2010

- Deferred pediatric study for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from 2 through < 18 years of age. Using doses selected based on the substudy listed under item 1 above, conduct a pediatric safety and efficacy study of telbivudine with efficacy based on virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

    - Protocol Submission: March, 2010
    - Study Start Date: September, 2010
    - Final Report Submission: September, 2013

- Deferred submission of pediatric PK dose selection and efficacy studies in patients from birth to < 2 years of age because these pediatric studies should be delayed until additional safety or effectiveness data have been collected. We anticipate waiting for completion and review of studies in pediatric patients 2 to < 18 years age before determining whether it is appropriate to study telbivudine for HBV in the birth to < 2 years age group. According to experts in pediatric HBV disease (pediatric hepatologists), treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this group may be waived in the future if this continues to be the consensus at the time the safety data are available or if the risk/benefit assessment is not favorable based on safety data from older pediatric patients.

    - Protocol Submission: January, 2013
    - Study Start Date: March, 2013
    - Final Report Submission: September, 2016

2. Recommended Post-Marketing Commitments

- Develop a dosing cup for distribution with Tyzeka oral solution that has clearly marked units of measure and contains only those units that correspond to dosing recommendations.

    - sNDA Submission: January 2010

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/s/

Mary Singer
4/28/2009 03:28:51 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-011 S-001 and 22,154
Submission Code	S-0053
Letter Date	December 21, 2007
Stamp Date	December 21, 2007
PDUFA Goal Date	October 21, 2008
Reviewer Name	Mary Singer, MD PhD
Review Completion Date	October 17, 2008
Established Name	Telbivudine (LdT)
(Proposed) Trade Name	Tyzeka®
Therapeutic Class	Antiviral Drug
Applicant	Novartis
Priority Designation	S
Formulation	600 mg tablets and oral solution
Dosing Regimen	600 mg orally daily
Indication	Treatment of chronic Hepatitis B
Intended Population	Adults

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends that a Complete Response be issued for NDA 22,154 at this time. For NDA 22-011 S-001, the Medical Officer recommends that submission of a Risk Evaluation and Mitigation Strategy (REMS) and MedGuide be considered a major amendment and that no action on the efficacy supplement be taken at this time. These recommendations are based on two major issues:

a. For NDA 22,154, the applicant proposed a new dosing regimen for patients with end stage renal disease (ESRD) for the oral formulation of telbivudine on September 19, 2008. Additional information is needed for review of———————— b(4)

b. A REMS including a Medication Guide is required for both NDA 22-011 S-001 and NDA 22-154 because of new safety information regarding peripheral neuropathy which will be included in the final product labeling for Tyzeka. The REMS and Medication Guide needs to be fully reviewed by the Division, the Safety Review Team and other consultants prior to approval of NDA 22-154 and NDA 22-011 S-001.

   The applicant has already distributed a Dear Healthcare Provider Letter regarding the new safety information on peripheral neuropathy observed with telbivudine alone or in combination with pegylated interferon-alfa-2a, so there is no urgency to release a new package insert with this information immediately, pending submission of a REMS and MedGuide to NDA 22-011 S-001, and subsequently to NDA 22-154.

For the efficacy supplement, NDA 22-011 S-001, the applicant has provided substantial evidence of effectiveness of telbivudine for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent serum aminotransferase elevation or histologically-active disease. Evidence for effectiveness was provided from a single large multicenter, randomized, double-blinded study, NV-02B-007 in which telbivudine was found to non-inferior to lamivudine for treatment of HBeAg-positive and HBeAg-negative hepatitis B, based on the primary endpoint, Therapeutic Response and for the key secondary endpoint, histological response at week 52. In this supplemental NDA 22-011 S-001, evidence of longer term telbivudine efficacy was demonstrated. Telbivudine was found to be non-inferior to lamivudine on the endpoint of Therapeutic response at week 104 (a secondary endpoint for that timepoint); however, histologic response was not measured at that time.

A second phase 3 study, NV-02B-015 was also submitted for evaluation of safety and efficacy with this supplemental NDA. This was a randomized, double-blinded study of telbivudine vs. lamivudine for treatment of chronic hepatitis B in Chinese patients. The study design was similar to that of the pivotal study, NV-02B-007, with two notable exceptions. Liver histology was not

evaluated as an outcome measure to confirm the virologic, serologic and biochemical surrogate markers for treatment response, and the primary endpoint was reduction of HBV DNA from baseline (rather than Therapeutic Response as measured in the pivotal study). The primary endpoint was analyzed at 52 weeks, and outcomes at 104 weeks were considered secondary. Because this study did not evaluate histologic response, and used a different primary endpoint than the pivotal study, it was reviewed as a supportive study for efficacy, as well as for safety. Additionally, the population studied was limited to Chinese patients and the results may not be fully generalizable to the U.S. population, and clinical trial sites for this study were not FDA-inspected to assess data quality and integrity. Virologic, serologic and biochemical outcomes in NV-02B-015 were similar to those obtained in study NV-02B-007.

Telbivudine was found to be safe for this indication in adult patients with chronic hepatitis B with compensated liver disease on the basis of safety data from 680 patients exposed to telbivudine for up to 104 weeks in studies NV-02B-007, with supportive safety data from an additional 167 patients exposed to telbivudine for up to 104 weeks in study NV-01B-015. Safety issues with telbivudine identified previously in Dr. Charlene Brown's review of October, 2006 at the time of approval included creatine kinase (CK) elevation, myopathy, ALT flares, as well as adverse events associated with this class of nucleoside analogues, including lactic acidosis with severe hepatomegaly and steatosis, and acute exacerbation of hepatitis B upon treatment discontinuation. In addition to those safety findings, in this review peripheral neuropathy was identified as a new safety concern with telbivudine alone or in combination with pegylated interferon alfa-2a; and the proposed labeling includes a new Warning for peripheral neuropathy. [redacted] has not been demonstrated. b(4)

NDA 22,154 for telbivudine oral solution, a new formulation, was cross-referenced to NDA 22,011 S-001 with regards to safety and efficacy. CMC review of this NDA revealed no issues precluding approval for the oral solution formulation. [redacted] in addition to the proposed doses for other patients with renal impairment. A Complete Response action is recommended for this NDA because of this deficiency, and because of the need for a REMS and MedGuide with the new safety information regarding telbivudine. b(4)

1.2 Risk Benefit Assessment

Chronic hepatitis B affects more than 400 million people worldwide and is considered a major public health problem globally. In some proportion of patients, untreated chronic hepatitis B may progress to cirrhosis, liver failure and death, and/or hepatocellular carcinoma. There are currently 7 approved drugs for the treatment of chronic hepatitis B including interferon-alfa and pegylated interferon-alfa-2a, and nucleoside or nucleotide analogues with direct antiviral activity against hepatitis B, including lamivudine, adefovir, telbivudine, tenofovir, and entecavir. As reviewed by Lau and Bleibel (2008), pegylated interferon has been associated with the highest rates of HBeAg and HbsAg seroconversion at one year (30%), but in general, interferons are not well-tolerated in adults, and have been associated with a significant adverse event profile, particularly for long-term use. The nucleosides and nucleotide analogues approved for treatment of hepatitis B all have similar efficacy, and in general, the nucleosides and nucleotides are better tolerated

than interferons; however, the durability of treatment response with these drugs may be limited by emergence of mutations in the HBV polymerase resulting in drug resistance, and cross-resistance to other agents. The highest levels of drug resistance had been observed with prolonged lamivudine treatment. Because of emerging resistance with increased use of lamivudine and other anti-HBV drugs since the initial approval of lamivudine in 1998, it is important to have a number of different anti-HBV agents with different resistance profiles available for treatment of drug-resistant HBV. The results of the pivotal trial for telbivudine reviewed for NDA 22-011 S-001, indicate that telbivudine resistance approaches 22% by the end of two years telbivudine treatment, and that telbivudine is cross resistant to lamivudine.

Nucleoside analogues for treatment of hepatitis B have been associated with a number of unfavorable class effects, most importantly, lactic acidosis, and severe hepatomegaly with hepatic steatosis, as well as severe acute exacerbations of hepatitis B after treatment discontinuation. Nucleosides approved for treatment of HIV have been associated with other toxicities, including peripheral neuropathy (particularly didanosine [ddI], stavudine [d4T], and zalcitabine [ddC]), myopathy (particularly zidovudine, [AZT]), pancreatitis, and effects on hematological parameters (anemia, leukopenia, neutropenia), lipid metabolism, lipodystrophy, and lipoatrophy.

In the review of safety for the initial approval of telbivudine in October, 2006, Dr. Charlene Brown found that in general, the tolerability and safety of telbivudine and lamivudine were similar based on 1 year of treatment, but also identified the following safety issues: CK elevation, and myopathy (associated with CK elevation). These adverse events are included in the Warnings section of the approved label, and are included in the Warnings and Precautions section of the proposed telbivudine label for the efficacy supplement. Hematologic adverse events, pancreatitis, lactic acidosis, hepatic steatosis, or adverse effects on lipid metabolism were not identified as significant risks with telbivudine based on the 1 or 2 year safety data. However, in this review, peripheral neuropathy was identified as a new safety signal based on postmarketing reports and adverse event reports from a clinical study, CLDT600A2406, which evaluated telbivudine alone in comparison to telbivudine plus pegylated interferon-alfa-2a and to pegylated interferon alone. Information regarding peripheral neuropathy is included in the Warnings and Precautions section of the proposed telbivudine label. Additionally, this new safety information has triggered a REMS, which will include conversion of the currently approved Patient Package Insert to a MedGuide, as well as a timetable for assessment.

Because of the requirement for a REMS and MedGuide due to new telbivudine safety information which will be included in the final product labeling, additional time is need for review of a REMS and MedGuide to NDA 22-011 S-001 prior to an action on the supplement. Overall, the risk/benefit of telbivudine appears favorable; however, because a number of nucleoside or nucleotide analogues are approved for treatment of chronic hepatitis B in adults, clinicians will need to choose an agent based on a risk/benefit analysis for individual patients, taking into account the safety profile of the agent, the baseline resistance profile of the HBV isolate, and the likelihood of developing resistance and cross-resistance with a particular agent.

1.3 Recommendations for Postmarketing Risk Management Activities

Because a REMS and Medication Guide must be submitted and reviewed prior to approval for NDA 22-154, and because an action on NDA 22-011 S-001 is deferred at this time, this section is not applicable.

1.4 Recommendations for other Post Marketing Study Commitments

Because a REMS and Medication Guide must be submitted and reviewed prior to approval for NDA 22-154, and because an action on NDA 22-011 S-001 is deferred at this time, this section is not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Tyzeka™ (telbivudine) is a synthetic thymidine nucleoside analogue (an HBV nucleoside analog reverse transcriptase inhibitor) with activity against hepatitis B virus (HBV). Telbivudine (LdT) is the unmodified β-L enantiomer of thymidine, the naturally occurring nucleoside. For further details on the chemical structure, formulations, and stability, see CMC review by Dr. Andrew Yu.

Tyzeka was initially approved October 25, 2006 for treatment of chronic HBV in adults and adolescents (≥ 16 years of age). The currently approved dosage form and strength for Tyzeka is a 600 mg tablet. For NDA 22-011 S-001, no changes in the Tyzeka tablet formulation or dosing for adults (with or without renal impairment) were proposed, rather updated information on longer term (104 week) safety and efficacy of telbivudine was provided. However, for NDA-22,154, a new oral formulation previously shown to be bioequivalent to the Tyzeka 600 mg tablet, was proposed for use in patients with renal impairment and in other adults or adolescents ≥ 16 years of age unable to swallow the tablet formulation. The safety and efficacy of Tyzeka has not been evaluated in patients < 16 years old. New dosing regimens for the oral formulation were proposed based on patient's creatinine clearance, as shown in the following table.

Table 1. Proposed Dosing for Patients with Renal Impairment

Creatinine Clearance (mL/min)	Telbivudine Oral Solution (20 mg/mL)	Telbivudine Tablet[a] (600 mg)
≥ 50	30 mL once daily	1 tab every 24 hours
30-49	20 mL once daily	1 tab every 48 hours
< 30 (not requiring dialysis)	10 mL once daily	1 tab every 72 hours
End Stage Renal Disease[1]	[redacted]	1 tab every 96 hours

b(4)

[1] administer Tyzeka after dialysis
[a] Currently approved dosing for renal impairment

Medical Officer Comments: *The proposed* [redacted] b(4)
was proposed in an amendment submitted on September 19, 2008. Additional information is needed by the Clinical pharmacology reviewers to review this proposal. [redacted] b(4)

These are considered deficiencies for NDA 22-154.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table shows the currently approved medications approved for treatment of chronic hepatitis B.

Table 2. Currently FDA-Approved Medication for Treatment of Chronic HBV

Approved Drug	Dosage Form	Approved Dosing Regimen for HBV Treatment	Year of Approval
Interferon-alpha 2b (Intron A)	Solution for injection; powder for injection/reconstitution	3 million IU/m2 3 times weekly for 1 week, then 6 million IU/m2 3 x weekly (subcutaneous or intra-muscular)	1992
Lamivudine	100 mg tablets	100 mg orally daily	1998
Pegylated interferon-alfa-2a (Pegasys)	180 µg single use vial (1.0 mL)	180 µg once weekly (subcutaneous)	2005
Adefovir	10 mg tablets	10 mg orally daily	2002
Entecavir	0.5 mg tablets 1.0 mg tablets 0.05 mg/mL oral solution	0.5 mg orally daily for treatment-naïve patients; 1.0 mg orally daily for lamivudine-refractory or known lamivudine or telbivudine resistance mutations	2005
Telbivudine	600 mg tablet	600 mg orally daily	2006
Tenfovir disoproxil fumarate	300 mg tablets	300 mg orally daily	2008

2.3 Availability of Proposed Active Ingredient in the United States

Tyzeka (telbivudine) is currently marketed and available in the U.S. From initial marketing in 2006 to the end of year 2007, more than [redacted] prescriptions were dispensed from U.S. retail pharmacies; and since marketing in 2006 through May 2008, more than [redacted] prescription were dispensed from U.S. retail pharmacies, as compiled by Vicky Borders-Hemphill, Pharm.D., of the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology, in her consultation regarding Tyzeka drug use. Dr. Hemphill concluded that Tyzeka use is steadily increasing from marketing through May 2008. b(4)

Since marketing in 2006, there have been no labeling revisions for Tyzeka.

2.4 Important Safety Issues with Consideration to Related Drugs

It is important to note that anti-HBV nucleoside or nucleotide analogs, including lamivudine, entecavir, adefovir and tenofovir, have been associated with lactic acidosis, hepatic steatosis and severe hepatomegaly. Additionally, all of the oral agents approved for treatment of chronic hepatitis B have been associated with severe acute exacerbations of hepatitis B upon treatment discontinuation. Class labeling for all of the oral anti-HBV drugs, including telbivudine, includes a Boxed Warning for these safety issues.

The following table shows additional safety considerations for use of telbivudine as well as for the other approved drugs for treatment of chronic HBV. The safety profile for telbivudine differs somewhat from the other approved drugs in this class (nucleoside and nucleotide analogues) in that CK elevations, sometimes in association with myopathy or other musculoskeletal adverse events are relatively common. In telbivudine clinical trials, myopathy and peripheral neuropathy were relatively uncommon (see Sections 5.3 Individual Studies and Section 7 Integrated Review of Safety), and have been described with other nucleoside analogues used for treatment of HIV. For example, zidoudine (AZT) has been associated with myopathy; and DDI, DDC and D4T have been associated with peripheral neuropathy.

Table 3. Safety Considerations with Drugs Approved for HBV Treatment

Approved Drug	Safety Issues
Interferon-alpha 2b (Intron A)	Poorly tolerated due to adverse event profile*
Pegylated interferon-alfa-2a (Pegasys)	Poorly tolerated due to adverse event profile*
Lamivudine	Emergence of resistance; acceptable tolerability
Adefovir	Dose-related renal toxicity; relatively low potency
Entecavir	Dose-related carcinogenicity in animals; potential teratogenicity; otherwise acceptable tolerability
Tenfovir disoproxil fumarate	Renal impairment; decrease in bone mineral density
Telbivudine	CK elevations, myopathy, peripheral neuropathy

*flu-like symptoms, fever, malaise, myalgias; and autoimmune disorders

***Medical Officer Comments**: Lamivudine is generally well-tolerated, but has been associated with pancreatitis. The biggest issue in the use of lamivudine for treatment of chronic HBV appears to be emergence of resistance. As discussed further in Section 4.2 Microbiology, emergence of resistance with telbivudine over the long term also appears to be an issue with this drug.*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A description of the pre-NDA regulatory activity for this product was summarized by Dr. Charlene Brown, in her Clinical Review of October 25, 2006. Since the approval of the original NDA 22-011 for Tyzeka in October, 2006, the applicant requested a pre-supplemental NDA meeting on July 13, 2007. The questions submitted by the applicant with that request and subsequent FDA response on August 13, 2007 are summarized below.

Sponsor's Question 1. Based on the data and approach summarized, does the Agency agree with the proposed labeling changes to the Tyzeka Label? (This question was in regard to claims of _____, being removed from the Tyzeka label. The sponsor summarized the results which supported a _____ claim in the label). b(4)

FDA Response: *We are unable to comment on your proposed labeling changes to the Tyzeka label based on your preliminary summary of data. Your proposed changes to the Tyzeka label are a review issue and will be addressed during the review of the supplementary NDA.* _____

b(4)

The Agency will consider _____ b(4)

While a Summary of Clinical Efficacy will not be needed, an Integrated Summary of Safety will still be required for the sNDA. We look forward to receiving your Pre-sNDA briefing package.

Sponsor's Question 2: _____ b(4)

FDA Response: _____ b(4)

[redacted] b(4)

Sponsor's Question 3: Does the Agency agree with Idenix's approach to filing the Summary of Clinical Efficacy/Integrated Summary of Efficacy?

FDA Response: *Your proposed approach to filing the Summary of Clinical Efficacy/Integrated Summary of Efficacy is acceptable.*

Question 4: Does the Agency agree with Idenix's approach to filing the Summary of Clinical Safety/Integrated Summary of Safety?

FDA Response: *Your proposed approach to filing the Summary of Clinical Safety/Integrated Summary of Safety is acceptable. Please ensure that treatment-emergent adverse events and laboratory abnormalities includes the 30 day window following the last dose of study drug. In addition, please ensure that the safety information is presented, regardless of assigned relationship to study drug. In addition, please ensure that two year safety data is also provided and analyzed for the NV-02B-007 trial and NV-02B-015 studies separately, in addition to the combined safety database for the NV-02B-007 and NV-02B-015 studies.*

Question 5: Does the Agency agree that the proposed data cutoffs will be sufficient to support the safety analyses Idenix proposes to present in the Summary of Clinical Safety/Integrated Summary of Safety?

FDA Response: *Given the increasing frequency of death and other SAEs in both the NV-02B-011 and NV02B-022 trials, please extend your data cutoff date for these studies to July 30, 2007 or later, if possible.*

Question 6: Does the Agency agree with the approach described above for submitting case report forms and individual patient profiles?

FDA Response: *Your described approach for submitting case report forms is acceptable. Please also provide case report forms or a narrative discussion of events for subjects who met the criteria that you outlined for submission of individual patient profiles. Please also submit case report forms for all deaths, regardless of causality. If you will be providing supportive safety data for NV-02B-022, then please also provide case report forms for subjects in that study who meet the criteria for the other trials.*

Clinical Pharmacology

Question 7: Does the Agency agree that the submission of the complete clinical study report would be sufficient to support the inclusion of this new drug-drug interaction data into the label?

FDA Response: *Yes.*

Clinical Microbiology

Question 8: Does the Agency foresee the need to submit additional data to support the

b(4)

FDA Response:

At the time of the initial approval for Tyzeka in October, 2006, pediatric studies in patients 0 to 16 years old were deferred under section 2 of the Pediatric Research Equity Act (PREA). A Written Request for pediatric studies in children 2-16 years old was issued subsequent to the action date on December 1, 2006. The Written Request was amended on July 24, 2007 (Amendment 1), and the sponsor requested additional changes on September 25, 2007. In response, the Division accepted the sponsor's proposa[illegible] b(4)
, but maintained the request for a
[illegible]d the request for

With the submission of NDA 22, 154, which is cross-referenced to NDA 22-011 S-001, the applicant has requested b(4)
a deferral consistent with the deferral granted upon approval of the telbivudine tablet formulation on October 6, 2008.

Medical Officer Comments: *We anticipate that studies in younger patients (< 2 years of age) will be deferred until after dose selection and safety have been established in older age groups.*

b(4)

No advisory committee meetings were held for the original NDA 22-011 for telbivudine.

2.6 Other Relevant Background Information

Since 2006, telivudine has been approved in 62 coutries worldwide with under the trade name, Sebivo, or as Tyzeka in the U.S.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

As reviewed by Dr. Charlene Brown in her clinical review of October 25, 2006, a number of on-site investigations were performed by the FDA Division of Scientific Investigations (DSI) for the

original telbivudine NDA 22-011. Four foreign clinical sites for the pivotal study, NV-02B-007 were audited and DSI inspections did not reveal any findings that might compromise the integrity of the data submitted with the NDA. No additional DSI inspections were performed for this supplemental NDA 22-011 S-001. For NDA 22-154 for the new oral formulation, all of the manufacturing sites passed FDA inspection.

The quality of the submission was somewhat disorganized in that the study report and datasets for the pivotal study, NV-02B-007 were submitted prior (July 26, 2007) to the supplemental NDA submission on December 21, 2007. Additional data for study NV-02B-007 were also submitted at the time of the supplemental NDA. This made it difficult for reviewers to locate specific data from that study. Additionally, NDA 22,154 was cross-referenced to NDA 22-011 S-001, and contained additional clinical information needed for review, including the drug-drug interaction study, NV-02B-028, clinical pharmacology information regarding proposed dosing, and the requests for pediatric waiver and deferral. Of even greater concern regarding submission quality was the late submission on September 19, 2008 of Clinical Pharmacology information regarding a new proposed [redacted] This information was included as an appendix to the applicant's response to CMC comments, and was not readily identified as an amendment to the NDA 22-154 for timely review. b(4)

3.2 Compliance with Good Clinical Practices

According to the sponsor, all clinical studies were conducted in accordance with the International Committee on Harmonization (ICH) Good Clinical Practice (GCP) standards. All clinical trial subjects provided informed consent in writing prior to participation in study procedures.

Additionally, during the NV-02B-007 study, the applicant conducted 19 routine investigator site audits for compliance with the study protocol, local regulations, and guidelines, as well as ICH GCP guidelines and to assess the quality of documentation.

3.3 Financial Disclosures

For NDA 22-011 S-001, the applicant provided a list of clinical investigators from studies NV-02B-007 and NV-02B-015 with nothing to disclose per 21 CFR part 54. Additionally, as reviewed previously by Dr. Charlene Brown in her clinical review of October 25, 2006, FDA form 3455 was filed for one investigator in the [redacted] trial, [redacted] received a research grant from Idenix to conduct [redacted] was the [redacted] for this [redacted] sub-study. Additionally, on [redacted] became an employee of Novartis Pharm Ag, based in Basel, Switzerland. This ,occurred, however, after his participation in study [redacted] had ended. b(6)

Medical Officer Comments: *It is not likely that any substantial bias would have arisen in [redacted] participation as a [redacted] in study [redacted] since treatment arms remained blinded throughout the study. Additionally,* [redacted] b(6)

population) were enrolled at [redacted] s study site numbe[redacted] and thus if any bias were introduced, the effect on overall study results would be minimal. b(6)

No financial disclosures for Study NV-02B-018 were identified in the December 21, 2007 or July 26, 2007 submission, or the amendment submitted on April 25, 2008. However, this study was not reviewed for efficacy, and safety information from this study is only considered supportive in this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Dr. Andrew Yu's review of Chemistry, Manufacturing and Controls (CMC) relevant to the new oral formulation proposed in NDA 22, 154. The CMC issues relevant to the tablet formulation were reviewed previously and no changes have been proposed to the tablet formulation in NDA 22-011 S-001. Dr Yu identified no issues with the manufacturing process or controls, specifications for the drug product or stability for the new formulation. The proposed shelf life of two years was considered acceptable. FDA inspection of all manufacturing sites revealed no manufacturing problems.

In the revised draft label submitted by the applicant on September 29, 2008, a statement regarding the sodium content for the Tyzeka oral formulation was proposed. According to the applicant, 30 mL of the oral solution of Tyzeka contains 600 mg telbivudine and 47 mg sodium (on average). In preliminary discussions with the CMC reviewer, Dr. Yu, the drug contains sodium sacchari[redacted] and sodium hydroxide. Most of the sodium in the oral formulation appears to come from the sodium hydroxide [redacted] The applicant's estimate of 47 mg sodium per 30 mL of the oral formulation appears to be within the range estimated from titration. Because the Tyzeka oral solution is to be used for dosing patients with renal impairment who may be on a sodium-controlled (or low sodium) diet, the applicant included this information [redacted] and in the Description section of the revised proposed label, submitted by email on September 29, 2008. b(4) b(4)

MedicalOfficer's Comments: *From a clinical standpoint, this reviewer has no objection to the addition of sodium content for the oral formulation in the Description section of the label.*

[redacted] b(4)

If this information is included in the final product labeling, it should also be included in the Information for Patients section, and in the Medication Guide.

4.2 Clinical Microbiology

For full details regarding Clinical Microbiology see Dr. Sung Rhee's review. This section briefly summarizes Dr. Rhee's findings regarding emergence of telbivudine with treatment over the first and second year of the NV-02B-007 study.

Genotypic analysis of paired baseline and on-treatment failure isolates from patients receiving telbivudine was conducted in 182/201 (90.5%) of patients with virologic failure (HBV DNA > 1000 copies/mL) by Year 2. The rtM204I/V substitutions emerged in 46 (including 35 with virologic rebound) during the first year, and in 96 (including 90 with virologic rebound) during the second year of telbivudine treatment. Thus rtM204I/V substitution was strongly associated with virologic failure in 142/201 (71%) patients and virologic rebound in 137/164 (83.5%) patients. The rtM204I substitution was the most frequent substitution, and was frequently found with substitutions rtL80I/V and rtL180M, and infrequently with rtV27A, rtL82M, rtV173L, rtT184I/S, rtA200V, rtL229F/V/W, and rtR289K. In addition, amino acid substitutions at position rtA181 (highly conserved among HBV isolates) were detected in 16 patients, and of these, 9 developed rtM204I/V substitutions.

Overall, the resistance profile for TBV appeared to be similar to that for LAM with the exception of rtM204V. The rtM204V substitution was infrequently detected in TBV-treatment failure patients (n=3). The cumulative probability of developing genotypic resistance to telbivudine was 7% at year 1 and 21.9% at year 2.

Medical Officer Comments: *Telbivudine resistance by 2 years treatment, approximately 22%, is similar to that of lamivudine resistance at 1 year with lamivudine treatment, at 15-30%. Because of the high resistance profiles of both lamivudine and telbivudine, neither is considered a preferred first-line agent for treatment of chronic HBV, as reviewed by Dienstag (2008).*

Additionally, Dr. Rhee reviewed the studies submitted for evaluation of potential mitochondrial toxicity with telbivudine. In summary, in study IDIX-07-116A there was minimal evidence of mitochondrial toxicity with telbivudine in primary human skeletal muscle cells after 6 days of treatment at concentrations up to 10 times the mean C_{max} in human plasma at the therapeutic dose; whereas the positive control, ddC, reduced mitochondrial DNA content and increased lactic acid production in these cells. Similarly, in study IDIX-07-116B, there was minimal evidence of mitochondrial toxicity in primary human hepatocytes after 6 days of treatment at concentrations up to 10-fold higher than the mean C_{max} value in human plasma at the therapeutic dose. However, the positive controls, AZT and ddC also showed no mitochondrial toxicity in these cells either, in contrast to previous findings in hepG2 cells (Study 02-CP-001a) where AZT inhibited lactate production and ddC decreased mitochondrial DNA content. In that study, there was no evidence for mitochondrial toxicity in hepG2 cells exposed to telbivudine at concentrations up to 10 μM for 14 days. Thus the study in primary human hepatocytes for the evaluation of the potential mitochondrial toxicity of telbivudine may not be valid because the positive controls were not positive in that study.

Medical Officer Comments: *The applicant will be encouraged to conduct additional studies to evaluate the potential for mitochondrial toxicity with telbivudine.*

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology or toxicology information was submitted with NDA 22-011 S-001 or NDA 22-154. Please refer to Dr. Ita Yuen's Pharmacology/Toxicology review of October,

2006. As summarized by Dr. Charlene Brown in her clinical review of October, 2006, spinal cord and sciatic axonopathy was observed in all telbivudine dose groups in monkey studies; however similar findings were noted in control animals, suggesting that these histopathological changes were probably not attributable to telbivudine. Repeat dose toxicity studies did not reveal lesions associated with skeletal muscle or heart muscle from monkeys or rats. No renal toxicity was observed in monkeys, mice, rabbits, or woodchucks; however, in rats, a slightly higher incidence of renal-associated death due to chronic progressive nephropathy was observed in male rats which received 1000 and 2000 mg/kg/day, and in female rats which received 2000 mg/kg/day telbivudine relative to controls. Chronic progressive nephropathy does not have a counterpart among the human diseases associated with renal failure, and the significance of these findings is not known. Renal toxicity has not been a significant safety finding in the clinical studies of telbivudine to date.

Telbivudine was not genotoxic in a battery of tests to assess genotoxicity, with and without metabolic activation. Additionally, telbivudine did not appear to be carcinogenic in rats or mice. In rabbit developmental toxicity studies, maternal toxicity (lower body weight and mean food consumption) was observed with receipt of telbivudine in comparison to controls, but no developmental toxicity was demonstrated in rabbits or rats at doses up to 1000 mg/kg/day. Additionally, doses up to 1000 mg/kg/day did not alter behavior, postnatal development, growth, sexual maturity, or fertility. The No Adverse Effect Level for reproductive toxicity was determined to be 1000 mg/kg/day.

4.4 Clinical Pharmacology

Please refer to Dr. Jenny Zheng's Clinical Pharmacology and Biopharmaceutics review of October, 2006 for detailed review of the pharmacokinetics, pharmacodynamics and exposure-response relationships of telbivudine. Additionally, see Dr. Zheng's review of October, 2008 for detailed review of NDA 22-154 for the new Tyzeka oral formulation. Dr. Zheng's findings are briefly summarized in this section.

4.4.1 Mechanism of Action

Tyzeka (telbivudine or LdT) is a synthetic nucleoside analogue with activity against hepatitis B virus polymerase (reverse transcriptase, rt) which is phosphorylated to its active metabolite telbivudine-5'-triphosphate by cellular kinases. Telbivudine-5'-triphosphate competes with the natural substrate, deoxythymidine-5'-triphosphate. Incorporation of telbivudine-5'-triphosphate into viral DNA causes chain termination, resulting in inhibition of HBV replication.

4.4.3 Pharmacodynamics

No new information on telbivudine pharmacodynamics was submitted for NDA 22-011 S-001 or NDA 22-154.

4.4.4. Pharmacokinetics

Tyzeka (telbivudine) is currently approved for treatment of chronic hepatitis B in the tablet formulation, with dose adjustment for renal insufficiency by increasing dosing intervals. Tyzeka oral solution, 20 mg/mL, was previously shown to be bioequivalent to the approved Tyzeka tablet. The applicant's initial proposal for use of the oral formulation for dosing in patients with renal impairment (creatinine clearance < 50 ml/min) was as follows:

Table 4. Proposed Dosing of Telbivudine Oral Solution in Patients with Renal Impairment

Creatinine Clearance (mL/min)	**Proposed Oral Solution Dose (20 mg/mL)**	**Approved Tablet Dose (600 mg)**
≥ 50	600 mg every 24 hrs	1 tablet every 24 hrs
30–49	400 mg every 24 hrs	1 tablet every 48 hrs
<30 (not requiring dialysis)	[redacted]	1 tablet every 72 hrs
ESRD	[redacted]	1 tablet every 96 hrs

b(4)

Based on the sponsor's submission of clinical pharmacology data for NDA 22-154 on December 21, 2007, the proposed dosing for the oral solution was found to be acceptable. However, on September 19, 2008, the applicant submitted new information and a new proposed [redacted]

b(4)

[redacted]

Medical Officer Comments: [redacted]

b(4)

[redacted] *is considered a deficiency for this submission, and a Complete Response will be issued for NDA 22-154.*

The applicant also submitted a drug interaction study with NDA 22-154, Study NV-02B-028. This was a phase 1, open-label, parallel group study to evaluate the potential for a pharmacokinetic drug-drug interaction between telbivudine and tenofovir disoproxil fumarate (TDF, Viread®). Dr. Zheng concluded that there was no significant impact of TDF on LdT pharmacokinetics and no statistically significant impact of LdT on TDF pharmacokinetics following repeated once-daily administration.

5 Sources of Clinical Data and Review Strategy

5.1 Tables of Clinical Studies

Clinical studies submitted for review with this NDA 22-011 S-001 include NV-02B-007 (study report and datasets submitted prior to the efficacy supplement on July 26, 2007, study report addendum submitted December 21, 2007), NV-02B-015 (submitted with efficacy supplement on December 21, 2007), NV-02B-018 (study report submitted July 26, 2007, and datasets submitted with efficacy supplement). Additionally in this submission, the applicant submitted a synopsis of the ongoing studies, NV-02B-011 and NV-02B-022 with narratives for deaths and serious or significant adverse events, and other preliminary safety data.

Studies evaluated for efficacy in this review include NV-02B-007, the pivotal study, and NV-02B-015, the supportive study. Study NV-02B-018 was not reviewed for efficacy, as discussed further in section 5.3 below. For evaluation of safety, studies NV-02B-007 and 015 were reviewed separately and as pooled safety data. Safety data from study NV-02B-018 was reviewed separately. For the ongoing study, NV-02B-022, which was the rollover study from other phase 2 and 3 telbivudine studies, evaluating long-term efficacy of open-label telbivudine, preliminary safety data was reviewed with regard to deaths, serious adverse events, discontinuations due to adverse events and significant adverse events. For the ongoing study, NV-02B-011, study data remained blinded to treatment, so a detailed safety analysis was not performed for this review. The following table summarizes the clinical studies submitted for efficacy and/or safety review.

Table 5. Clinical Studies Submitted for Review of Efficacy with NDA 22-011 S-001

Listing of Clinical Studies

Type of Study	Study Identifier[1]	Location of Study Report[2]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
5.3.1 Reports of Biopharmaceutic Studies									
No New information included in two year safety and efficacy application.									
5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials									
No New information included in two year safety and efficacy application.									
5.3.3 Reports of Human Pharmacokinetic Studies									
No New information included in two year safety and efficacy application. Cross reference is made to oral solution (20 mg/mL) application for data to support new PK data in proposed label									
5.3.4 Reports of Human Pharmacodynamic Studies									
No New information included in two year safety and efficacy application.									
5.3.5 Reports of Efficacy and Safety Studies									
Safety & Efficacy	NV-02B-007	5.3.5.1	Long Term Safety & Efficacy	Randomized, double blind, active controlled telbivudine vs LAM	3 tablets telbivudine; 200 mg; QD; Oral	1378 (enrolled); 1367 (ITT)	Adults with HBeAg-Positive and HBeAg-Negative Compensated Chronic Hepatitis B	104 weeks	Complete; Full CSR plus Addendum (study report body only)[3]
Safety & Efficacy	NV-02B-015	5.3.5.1	Long Term Safety & Efficacy in Chinese Patients	Double blind, randomized, active controlled telbivudine vs LAM	3 tablets telbivudine; 200 mg; QD; Oral	332	Chinese Adults with Compensated Chronic Hepatitis B; HBeAg- and HBeAg+ patients	104 weeks	Complete; Full CSR plus Addendum (study report body only)[3]

Type of Study	Study Identifier[1]	Location of Study Report[2]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Analyses of results across multiple studies (ISS-pooled tables)	SRAS	5.3.5.3	Supportive tables for Efficacy and Safety	N/A[4]	N/A[4]	N/A[4]	N/A[4]	N/A[4]	NA[4] Supportive tables for SCS
Safety & Efficacy	NV-02B-011	5.3.5.4	Long Term Safety & Efficacy	Randomized, double blind, active controlled telbivudine vs LAM	3 tablets telbivudine; 200 mg; QD; Oral	232	Adults with Decompensated Chronic Hepatitis B; HBeAg- and HBeAg+ patients	104 weeks	Ongoing; Addendum (study report body only)[3]
Safety & Efficacy	NV-02B-018	5.3.5.4	Drug Comparison (ADV); Safety & Efficacy	Randomized, Open label telbivudine vs ADV	3 tablets telbivudine; 200 mg; QD; Oral	136	Adults with HBeAg-Positive, Compensated Chronic Hepatitis B	52 weeks	Complete; Full CSR plus Addendum (study report body only)[3]
Safety & Efficacy	NV-02B-022	5.3.5.4	Long Term Safety & Efficacy	Open Label - telbivudine rollover from Idenix-sponsored telbivudine studies	3 tablets telbivudine; 200 mg; QD; Oral	1873	Adults with Chronic Hepatitis B; HBeAg- and HBeAg+ patients	104 weeks	Ongoing; Addendum (study report body only)[3]

Source: Tabular Listing of Clinical Studies, CTD 5.2

Virologic data for evaluation of HBV resistance and other virologic parameters were reported separately from the clinical studies. Additional Microbiology studies submitted with this efficacy supplement are shown in the following table.

Table 6. Microbiology Studies submitted with NDA 22-011 S-001

Type of Study	Study Identifier[1]	Location of Study Report[2]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Antiviral	IDIX-07-151	5.3.5.4	Microbiology studies: *in vivo* studies; Week 104 resistance analysis of patients from NV-02B-007	Direct sequencing of HBV polymerase RT domain	3 tablets telbivudine; 200 mg; QD; Oral	1367 (ITT) samples including: genotype C= 692 genotype B= 360 genotype D= 217 genotype A= 81 genotype others= 17	Adults with HBeAg-Positive and HBeAg-Negative Compensated Chronic Hepatitis B	N/A[6]	Complete: Antiviral report
Antiviral	IDIX-07-208	5.3.5.4	Clinical predictors of resistance	N/A[7]	3 tablets telbivudine; 200 mg; QD; Oral	1367 (ITT)	Adults with HBeAg-Positive and HBeAg-Negative Compensated Chronic Hepatitis B	N/A[6]	Complete: antiviral report

Type of Study	Study Identifier[1]	Location of Study Report[2]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Antiviral	IDIX-08-140	5.3.5.4	Microbiology studies; *in vivo* studies; Week 48 resistance analysis of patients from NV-02B-015	Direct sequencing of HBV polymerase RT domain	3 tablets telbivudine; 200 mg; QD; Oral	332 samples including: genotype C= 210 genotype B= 120 genotype others= 2	Adults with HBeAg-Positive and HBeAg-Negative Compensated Chronic Hepatitis B	N/A[6]	Complete; Antiviral report
Antiviral	IDIX-07-200	5.3.5.4	Microbiology studies; *in vivo* studies; Week 104 resistance analysis of patients from NV-02B-015	Direct sequencing of HBV polymerase RT domain	3 tablets telbivudine; 200 mg; QD; Oral	332 samples including: genotype C= 210 genotype B= 120 genotype others= 2	Adults with HBeAg-Positive and HBeAg-Negative Compensated Chronic Hepatitis B	N/A[6]	Complete; Antiviral report

1 The text in the Study Identifier column is linked to the associated study report.
2 Folder in the CTD in which the study is located.
3 For completed studies, an Addendum (stud-report body only) to the final CSR contains supplementary safety and/or efficacy tables
4 Not applicable (N/A); SRAS document contains pooled (007+015 studies) Week 104 post text tables to support 2.7.4-summary of clinical safety
5 Addendum: For ongoing studies, an Addendum to the original stud-report-body contains supporting safety and/or efficacy
6 Not Applicable (N/A) as there is no treatment of patients in this study, only analysis of samples
7 Not Applicable (N/A) as the report presents clinical predictors analyses of resistance data from patients in NV-02B-007 and report IDIX-07-151

Source: Tabular Listing of Clinical Studies, CTD 5.2

Additional sources of data for this review include the 120-Day Safety Update (submitted on May 30, 2008), the Periodic Safety Update Report 3 (submitted October 31, 2007), AERS postmarketing safety data obtained in consultation with the Office of Safety and Epidemiology (OSE), revised draft labeling (submitted May 30, 2008), additional safety datasets for studies 007 and 015 (submitted June 6, 2008), and the addendum to study report for NV-02B-018 (submitted May 22, 2008). Additional sources of information for this review were obtained from the literature searches by the applicant and reviewer.

5.2 Review Strategy

The approval of telbivudine in October, 2006 was based on 52-week efficacy data from study NV-02B-007. For this review, the 104 week data from this study was considered the primary source of efficacy data for this application to confirm longer term efficacy of this product. The applicant also submitted study NV-02B-015 as a confirmatory study for telbivudine efficacy; however for this review, the 52 and 104 week efficacy data from study 015 were considered as supportive rather than confirmatory for this application, largely because histological response was not measured as an outcome at any time in this study which was conducted solely in Chinese patients for the purpose of Chinese regulatory review. Additionally, the primary endpoint for study 015 differed from that used to assess efficacy of telbivudine in study 007. Thus, although studies 007 and 015 were very similar in design, efficacy data were evaluated separately for this review and were not pooled.

For this review, efficacy and safety data from studies 007 and 015 are reviewed as individual studies, in section 5.3. Study 018 was reviewed only briefly for efficacy because it was a small open-label study which compared telbivudine to adefovir with the primary endpoint at 24 weeks in HBeAg-positive patients with chronic hepatitis B. Additionally, liver histology was not used for study entry or as a study outcome measure. A brief summary of the applicant's efficacy conclusions for study 018 are presented in section 5.3. Safety data from study 018 is reviewed in section 5.3. In section 6, a brief summary of efficacy conclusions from studies 007 and 015 are presented.

Section 7 contains a review of safety. For review of safety, the 52 week and 104 week data from studies 007 and 015 were reviewed separately in section 5.3. Pooled analyses of the 104 week safety data from studies 007 and 015 data are reviewed in section 7. Although the study populations were different, pooling the safety data from these two studies was considered acceptable because of the similarity in study designs, use of the same comparator (lamivudine), and similar exposures to telbivudine.

Safety data from study 018 is reviewed separately in section 5.3; and preliminary safety data from ongoing studies 011 and 022 are reviewed in Section 7.3 and in Section 7.7, particularly with regard to deaths, serious adverse events and significant adverse events. The 120-Day Safety Update also included safety data from the recently completed studies, 004 and 019, and safety updates from ongoing studies. Safety data from these studies is included in the review of the 120-Day Safety report in Section 7.7.

Postmarketing data for telbivudine was not submitted by the applicant with the efficacy supplement submitted on December 21, 2007 or with the 120-day safety update submitted on May30, 2008; however the applicant cross-referenced the most recent Periodic Safety Update Report (PSUR-3), submitted on October 31, 2007. Review of PSUR 3 is included in section 7.7 of this review.

Additionally, OSE was consulted for review of the postmarketing data on telbivudine submitted to AERS and for review of telbivudine drug use data. These consultation reports are summarized and discussed in section 7.7.

The Microbiology studies were reviewed in detail by Dr. Sung Rhee and Dr. Julian O'Rear. Please see Dr. Rhee's review for analysis review of telbivudine resistance data. Conclusions regarding telbivudine resistance are summarized in section 4.4.

5.3 Discussion of Individual Studies

This section contains review of efficacy and safety for the pivotal study, NV-02B-007, and brief review of efficacy and safety in Study NV-02B-015. Study NV-02B-018 is summarized briefly in this section, and safety data from that study is reviewed. Study NV-02B-028, the drug interaction study with telbivudine and tenofovir, is also briefly reviewed in this section.

5.3.1. Study NV-02B-007

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

Objectives: The primary objective of this study was to compare the efficacy and safety of telbivudine and lamivudine in adults with chronic hepatitis B (HBeAg-positive and HBeAg-negative) and compensated liver disease over a 2 year (104 weeks) period.

Primary Efficacy Endpoint: Therapeutic Response, defined as serum HBV DNA < 5 log10 copies/mL and HBeAg loss or ALT normalization. The principle treatment comparison was performed at Week 52.

Secondary Efficacy Endpoints: The key secondary endpoint was histological response, defined as ≥ 2 point reduction in Knodell necroinflammatory score, with no worsening of fibrosis. This endpoint was assessed only at Week 52.

Additional secondary endpoints included:

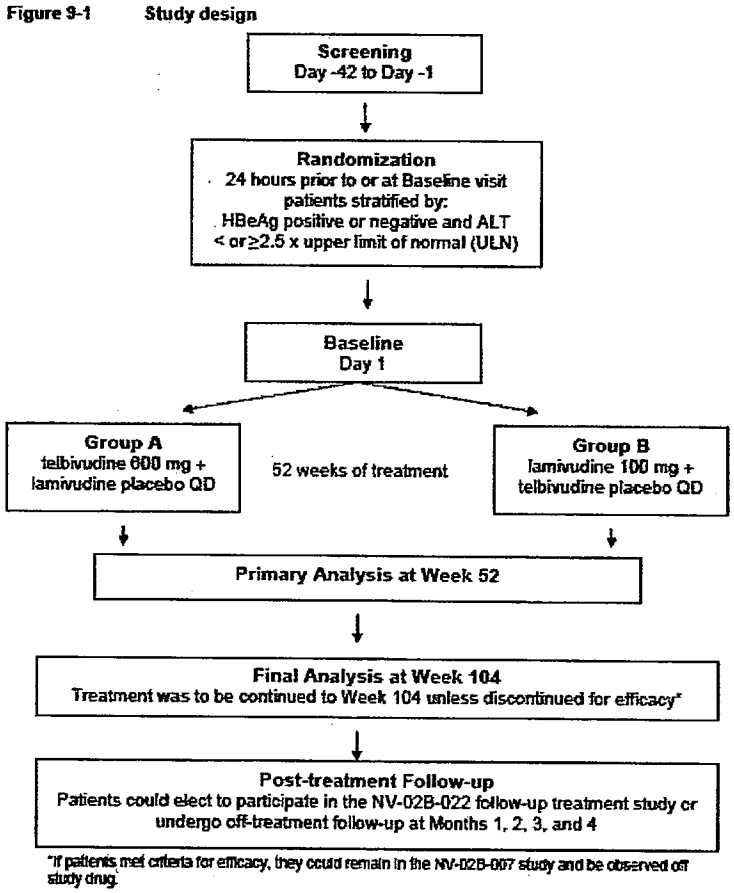
- Virologic Response: HBeAg loss and HBV DNA < 5 log10 copies/mL (for HBeAg-positive subgroups)
- Composite Serologic Response: HBV DNA < 5 log10 copies/mL and ALT normalization (in HBeAg-negative subgroups)
- HBeAg loss and HBeAg seroconversion (loss of HBeAg and gain of HBeAb) in HBeAg-positive subgroups
- ALT normalization, defined as ALT within normal limits on two successive visits for patient with elevated (≥ 1 x ULN) at baseline
- HBsAg loss and seroconversion (loss of HBsAg and gain of HBsAb)
- HBV DNA suppression: serum HBV DNA < 5 log10 copies/mL on two successive visits in a patients with HBV DNA ≥ 6 log10 copies/mL at baseline
- Changes in mean and median HBV DNA from baseline

- Proportion of patients achieving serum HBV DNA to specific levels (< 5, < 4, < 3 log10 copies/mL and non-detectable) by COBAS Amplicor PCR assay.
- Virologic Breakthrough (see definitions of virologic breakthrough below).

Multiple other pre-specified secondary endpoints were included in the protocol, such as maintained virologic response (virologic response documented on at least two consecutive visits and at last treatment visit, with no 2 intervening consecutive disqualifying values); and sustained virologic response (virologic response documented on at least two consecutive visits and at last study visit, with no 2 intervening consecutive disqualifying values), and many others. Results for all of the secondary endpoints were not reviewed in detail.

Study Design: Phase 3, randomized, double-blind, multicenter, active controlled study to compare antiviral activity and safety of telbivudine (600 mg/day) with lamivudine (100 mg/day) over 104 weeks of treatment. Patients were randomized 1:1 to receive either telbivudine or lamivudine, and were stratified by hepatitis B e antigen status (HBeAg-positive vs. HBeAg-negative) and by ALT level (ALT < 2.5 x ULN versus ALT ≥ 2.5 x ULN). The following figure from the applicant's study report shows the study design:

Figure 1. Study Design



Inclusion and Exclusion Criteria

In brief, male or female patients between the ages of 16 to 70 years old with documented chronic hepatitis B, i.e. HBsAg-positive with elevated serum ALT (1.3-10 x ULN) at screening, and liver biopsy within 12 months prior to randomization, with serum HBV DNA ≥ 6 log10 copies/mL at screening, could be enrolled in the study. Major exclusion criteria were pregnancy or lactation, co-infection with HIV, HCV or hepatitis D virus, prior receipt (at any time) of lamivudine or an investigational anti-HBV nucleoside or nucleotide, or receipt of an interferon for treatment of HBV in the 12 months prior to screening. Patients with hepatic decompensation or hepatocellular carcinoma (HCC) were excluded.

Study Procedures and Timelines

Enrolled patients were followed through study Week 104, and could be subsequently enrolled into the open-label long term telbivudine study, NV-02B-022, or were followed monthly for 4 months post-treatment. Additionally patients who discontinued study treatment prematurely for any reason were to be followed post-treatment for monthly visits for 4 months. The schedule of study visits and procedures is shown in the following table.

Table 7. Schedule of Evaluations in Study NV-02B-007

Table 3 Schedule of Evaluations

Evaluation	Screen	Baseline (Pre-dose)	Treatment Period by Weeks																Early Term/104
			2	4	8	12	16	24	32	40	48	52	60	68	76	84	92	100	
Informed consent	X																		
Review of Inclusion/Exclusion Criteria	X	X																	
Medical History/Review of Systems	X																		
Prior/Concurrent Medications Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X											X							X
Symptom-Directed Physical Examination		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	
Body Weight Measurements	X					X		X				X			X				X
Height Measurement	X																		
Vital Signs (HR and BP)	X	X				X		X				X			X				X
Serum Pregnancy Test (β-HCG)[1]	X																		
Urine Pregnancy Test		X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[1]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[1]
France only Urine Pregnancy Test		X[2]		X[1]	X[1]	X[2]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
AFP	X																		
HIV-1, HIV-2, HCV, HDV screens	X																		
Serum Chemistries and Liver Function[7] tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prothrombin time	X	X										X							X

Evaluation	Screen	Baseline (Pre-dose)	Treatment Period by Weeks																
			2	4	8	12	16	24	32	40	48	52	60	68	76	84	92	100	Early Term/104
Urinalysis	X	X						X				X							X
Serum for storage[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV serologies (HBsAg Ab and HBeAg Ab)	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X
Serum HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Biopsy	X[4]											X							
Study Drug Dispensation		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Accountability/Adherence			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge patient from IVRS																			X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]For females of childbearing potential.
[2]For females of childbearing potential if suggested by the patient's interval history.
[3]For potential additional testing (e.g., viral genotyping or repeat testing of specific analytes see section 7.2.3).
[4] Screening liver biopsy within 12 months prior to screening. If previous biopsy not available, pre-treatment liver biopsy must be done prior to randomization to confirm diagnosis of chronic hepatitis B.
[7]Serum Chemistries (Cr, TP, Amylase, Lipase, CK), AFP at Screen only; Liver Function tests (ALT, AST, ALB, TB)

Evaluation	Follow-Up[5]			
	Month 1	Month 2	Month 3	Month 4
Prior/Concurrent Medications Review	X	X	X	X
Symptom-Directed Physical Examination	X	X	X	
Full Physical Exam (including weight)				X
Vital Signs (HR and BP)	X	X	X	X
Serum Chemistries and LFTs[7]	X	X	X	X
Hematology Panel	X	X	X	X
Serum HBV DNA	X	X	X	X
HBV serologies (HBsAg/Ab and HBeAg/Ab)	X	X	X	X
Urine Pregnancy Test				X[6]
France only Urine Pregnancy Test	X[1]	X[1]	X[1]	X[6]
Serum for Storage[3]	X	X	X	X
Adverse Events	X	X	X	X

[1]For females of childbearing potential.
[3]For potential additional testing (e.g., viral genotyping or repeat testing of specific analytes, see section 7.2.3).
[5]For patients who discontinue study medication prior to Week 104 or who (at Week 104) elect not to participate in the follow-up protocol.
[6]At last anticipated follow-up visit, e.g., nominally Week 16 post-treatment for females of childbearing potential.
[7]Serum Chemistries (Cr, TP, Amylase, Lipase, CK), AFP at Screen only; Liver Function tests (ALT, AST, ALB, TB)

Source: Clinical Study Protocol NV-02B-007

Treatments: Patients were randomized to receive telbivudine 600 mg (as 3 x 200 mg tablets) plus 1 lamivudine placebo capsule or 1 lamivudine 100 mg capsule plus 3 LdT placebo tablets.

Study Sites: This was an international multicenter study. A total of 112 sites were enrolled in 20 countries.

Study Populations

The primary analysis population for efficacy and safety was the ITT population, defined as all randomized patients who received at least one dose of study medication and had at least one observation after baseline. The ITT population was also the safety population. The efficacy evaluation (EE) population consisted of all patients who received at least one dose of study drug and did not have major protocol violations with regard to key entry criteria. This review focuses mainly on the ITT population for evaluation of efficacy and safety.

Study NV-02B-007 was a non-inferiority study, with a pre-specified non-inferiority margin of

-15% in comparison to lamivudine.

Patient Disposition

A total of 1370 patients were randomized, but 3 had no baseline observations. These 3 patients were excluded from all analyses. The ITT (and safety) population included 1367 patients, 687 received lamivudine, and 680 received telbivudine. According to the applicant all patients received the drug to which they were assigned.

The secondary analysis population, the Efficacy Evaluable (EE) population at 104 weeks included 1314 patients, approximately 96% of the ITT population. In the lamivudine treatment group, 28 patients were excluded from the EE population; and 25 patients in the telbivudine group were excluded from the EE population.

The overall study discontinuation rate in the ITT population was 10.5% at 104 weeks in comparison to 4.2% at Week 52. In the ITT population at Week 104, 56/680 (8.2%) patients in the telbivudine group and 88 (12.8%) patients in the lamivudine group were discontinued from the study for any reason. More patients in the lamivudine treatment group were discontinued from the study for lack of efficacy after week 24 (16/687, 2.3%), in comparison to the telbivudine group (6/680, 0.9%). Additionally, more patients in the lamivudine treatment group were discontinued from the study due to adverse events (10/687 [1.5%] lamivudine vs. 5/680, [0.7%] telbivudine), clinical disease progression (2 lamivudine patients and no telbivudine patients), and request of patient, investigator or sponsor. There was one death (due to a traffic accident) in the study in a lamivudine-treated patient.

Medical Officer Comments: *No additional information regarding reasons for discontinuation was located in the datasets or study report regarding patients who were discontinued at the request of the sponsor, investigator, or themselves.*

In the EE population, more telbivudine-treated patients were discontinued from the study due to non-compliance, and more lamivudine treated patients were discontinued due to adverse events or lack of efficacy. Patient disposition is summarized in the following table.

Table 8. Patient Disposition to Week 104 in Study NV-02B-007

	Lamivudine		Telbivudine		Total	
Patient populations	N	(%)	N	(%)	N	(%)
Randomized patients	687	(100)	683	(100)	1370	(100)
ITT & Safety populations	687	(100)	680	(99.6)	1367	(99.8)
EE population	659	(95.9)	655	(95.9)	1314	(95.9)
Reason for study discontinuation	n	(%)	n	(%)	n	(%)
ITT & Safety populations - any reason	88	(12.8)	56	(8.2)	144	(10.5)
Noncompliance	6	(0.9)	8	(1.2)	14	(1.0)
Pregnancy	5	(0.7)	4	(0.6)	9	(0.7)
Adverse event	10	(1.5)	5	(0.7)	15	(1.1)
Clinical disease progression	2	(0.3)	0		2	(0.1)
Lack of efficacy after Week 24	16	(2.3)	6	(0.9)	22	(1.6)
Death	1	(0.1)	0		1	(0.1)
Request*	48	(7.0)	33	(4.9)	81	(5.9)
EE population - any reason	80	(12.1)	50	(7.6)	130	(9.9)
Noncompliance	4	(0.6)	8	(1.2)	12	(0.9)
Pregnancy	4	(0.6)	4	(0.6)	8	(0.6)
Adverse event(s)	8	(1.2)	4	(0.6)	12	(0.9)
Clinical disease progression	2	(0.3)	0		2	(0.2%)
Lack of efficacy after Week 24	15	(2.3)	6	(0.9)	21	(1.6%)

	Lamivudine		Telbivudine		Total	
Death	1	(0.2)	0		1	(0.1)
Request*	46	(7.0)	28	(4.3)	74	(5.6)

*Patient-, investigator-, or Sponsor-initiated request.

Source: Table 10-2 NV-02B-007 Study Report

In the applicant's analysis, the mean time to study withdrawal was 98 weeks in the lamivudine group and 116 weeks in the telbivudine group in the ITT population. Note that patients were to be treated for up to 104 weeks, and then followed for 4 months (16 weeks) post-treatment unless they rolled-over into the open-label telbivudine study, 022.

Medical Officer Comments: *Discontinuations due to adverse events are discussed in the review of safety for this study below.*

Protocol Exemptions and Deviations in the ITT/Safety Population

Similar proportions of patients in each treatment group, 47/687 (6.8%) in the lamivudine group, and 47/680 (6.9%) in the telbivudine group had protocol exemptions or deviations. Similar proportions of patients were excluded from the EE population due to non-compliance, 9/687 (1.3%) vs. 6/680 (0.9) in the lamivudine and telbivudine groups, respectively. A total of 12/687 (1.7%) in the lamivudine arm, and 9/680 (1.3%) in the telbivudine arm took a "prohibited" medication which disqualified subsequent data from the EE analysis. With the exception of one patient in each treatment group who received prohibited medications in the first year of the study, prohibited medications were received after Week 52. Among lamivudine-treated patients, adefovir dipivoxil was the prohibited medication in 11 patients, and one patient received lamivudine; while among the telbivudine-treated patients, 5 received adefovir dipivoxil, 1

received entecavir, 1 received zidovudine plus lamivudine, and two received systemic corticosteroids. Efficacy data for these patients was censored in the ITT population from the time the prohibited medication was initiated.

Medical Officer Comments: *Search of the concomitant medications dataset for this study, A_CONMED, confirmed that the prohibited medications listed above were administered while on-treatment in 12 lamivudine-treated and 9 telbivudine-treated patients, although it is not clear why lamivudine was a prohibited medication in the lamivudine group. One patient in the telbivudine group received combivir (lamivudine plus zidovudine) for prophylaxis, presumably HIV prophylaxis, although that was not specified.*

Patient Demographics in Study NV-02B-007

In this study, the median patient age was 34 years overall, ranging from 16 to 68 years old. Most patients were male (76% overall), and most were of Asian descent (76% overall). The treatment groups in the ITT population were generally well-balanced with regards to age, gender, race, height, and weight, as shown in the following table.

Table 9. Patient Demographics in Study NV-02B-007

Table 11-5 Demographic summary by treatment group – overall ITT population

Parameter	Lamivudine (N=687)	Telbivudine (N=680)	Total (N=1367)	*P*-value*
Age (years)				
Mean (SE)	36.2 (0.46)	35.5 (0.45)	35.8 (0.32)	0.2800
Median	35.0	34.0	34.0	
25%, 75%	26.0, 45.0	26.0, 44.0	26.0, 44.0	
Range	16.0, 68.0	16.0, 68.0	16.0, 68.0	
Gender, n (%)				
Male	528 (76.9)	507 (74.6)	1035 (75.7)	0.3220
Female	159 (23.1)	173 (25.4)	332 (24.3)	
Race, n (%)				
Caucasian	111 (16.2)	98 (14.4)	209 (15.3)	0.6858
Asian#	515 (75.0)	525 (77.2)	1040 (76.1)	
African/African/American	10 (1.5)	7 (1.0)	17 (1.2)	
Hispanic/Latino	8 (1.2)	4 (0.6)	12 (0.9)	
Middle East./Indian Subcontinent	11 (1.6)	14 (2.1)	25 (1.8)	
Other races	32 (4.7)	32 (4.7)	64 (4.7)	
Height§, (cm)				
Mean (SE)	168.3 (0.32)	168.4 (0.32)	168.4 (0.22)	0.8246
Median	169.0	169.0	169.0	
25%, 75%	162.6, 174.0	163.0, 174.0	162.9, 174.0	
Range	140.5, 198.0	132.1, 195.6	132.1, 198.0	
Weight†, (kg)				
Mean (SE)	69.4 (0.58)	67.8 (0.55)	68.6 (0.40)	0.0429
Median	68.0	66.0	67.0	
25%, 75%	59.0, 77.0	57.8, 75.0	58.1, 76.0	
Range	38.0, 149.7	38.0, 126.0	38.0, 149.7	

The applicant noted a statistical interaction between HBeAg status and the primary efficacy endpoint (Therapeutic Response at week 52). Patients who were HBeAg-negative were generally older (median age 43 years) than those in the HBeAg-positive population (median 30 years). Additionally, there were a higher proportion of HBeAg-negative males (79% overall) than HBeAg-positive males (74%), and a higher proportion of Asians who were HBeAg-positive (82%) than HBeAg-negative (65%). Correspondingly, there was a higher proportion of HBeAg-negative Caucasians (23%) than HBeAg-positive Caucasians (12%).

A total of 112 sites were enrolled in 20 countries. By continent, 62% all patients were enrolled in Asian countries, including China, Hong Kong, Singapore, Korea, Taiwan, Thailand, and India; 11% were enrolled in Oceania (Australia and New Zealand); 12% in North America (U.S. and Canada), and 15% in Europe (France, Germany, Spain, Greece, Italy, United Kingdom, Poland, Turkey, and Czech Republic). Study enrollment by country is shown in the following table.

Table 10. Enrollment by Country in ITT Population

Table 10-1 Summary of enrollment by country – ITT population

	Number of sites (N=112)	Lamivudine (N=687)		Telbivudine (N=680)		Total (N=1367)
Country (N=20)	n	HBeAg+ (N=463) n (%)	HBeAg- (N=224) n (%)	HBeAg+ (N=458) n (%)	HBeAg- (N=222) n (%)	n (%)
Australia	6	25 (5)	8 (4)	12 (3)	7 (3)	52 (4)
Canada	6	21 (5)	18 (8)	20 (4)	12 (5)	71 (5)
China	14	148 (32)	34 (15)	152 (33)	39 (18)	373 (27)
Czech Republic	4	5 (1)	4 (2)	6 (1)	7 (3)	22 (2)
France	8	8 (2)	6 (3)	10 (2)	7 (3)	31 (2)
Germany	3	14 (3)	5 (2)	11 (2)	10 (5)	40 (3)
Greece	2	2 (0)	9 (4)	1 (0)	2 (1)	14 (1)
Hong Kong	3	39 (8)	15 (7)	37 (8)	18 (8)	109 (8)
India	5	6 (1)	2 (1)	8 (2)	3 (1)	19 (1)
Italy	2	1 (0)	1 (0)	0	0	2 (0)
Korea	7	31 (7)	8 (4)	46 (10)	6 (3)	91 (7)
New Zealand*	3	28 (6)	20 (9)	19 (4)	26 (12)	93 (7)
Poland	3	2 (0)	4 (2)	4 (1)	3 (1)	13 (1)
Singapore	3	11 (2)	9 (4)	16 (3)	12 (5)	48 (4)
Spain	4	2 (0)	10 (4)	3 (1)	4 (2)	19 (1)
Taiwan	4	29 (6)	27 (12)	26 (6)	32 (14)	114 (8)
Thailand	5	33 (7)	16 (7)	39 (9)	11 (5)	99 (7)
Turkey	4	15 (3)	12 (5)	18 (4)	5 (2)	50 (4)
United Kingdom	3	5 (1)	3 (1)	2 (0)	4 (2)	14 (1)
United States*	23	38 (8)	13 (6)	28 (6)	14 (6)	93 (7)

HBeAg+ = HBeAg-positive; HBeAg– = HBeAg-negative
Note: Percentage totals may not be equal to 100 due to rounding
*Three investigators are listed twice in the source table, Dr. Sik To Lai (Hong Kong and New Zealand), and Drs. Han and Min (US) because one of their patients transferred to another investigative site.

Medical Officer Comments: *The 14 study sites in China enrolled the largest proportion of patients in this study (27% overall); while enrollment in the 23 U.S. sites comprised only 7% of the overall study population.*

Stratification by HBeAg Status and ALT level

At baseline, 685/687 (99.7%) lamivudine patients and 679/680 (99.8%) of telbivudine patients were HBsAg-positive; 1 lamivudine-treated patient was HBsAg-nonreactive. At baseline in the ITT population, based on laboratory data (Study 007 KEYCRF dataset), approximately two-thirds of patients in each treatment group were HBeAg-positive at baseline, 455/687 (66.3%) in the lamivudine group, and 445/680 (65.4%); while approximately one-third patients in each treatment group were HBeAg-negative, 232/687 (33.7%), and 235/680 (34.6%) for lamivudine and telbivudine groups, respectively. The following table shows the distribution of randomized patients in to strata based on HBeAg status and ALT level.

Table 11. Stratification of Analysis Population

Table 11-4 Stratification of overall ITT, EE and Safety populations based on HBeAg status and ALT levels – all randomized patients

	Lamivudine (N=687)			Telbivudine (N=683)		
	ITT	EE	Safety	ITT	EE	Safety
Stratification	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
HBeAg-positive ALT <2.5 x ULN	217 (31.6)	195 (28.4)	206 (30.0)	212 (31.0)	198 (29.0)	204 (29.9)
HBeAg-positive ALT ≥2.5 x ULN	246 (35.8)	243 (35.4)	249 (36.2)	246 (36.0)	232 (34.0)	241 (35.3)
HBeAg-negative ALT <2.5 x ULN	112 (16.3)	113 (16.4)	119 (17.3)	111 (16.3)	112 (16.4)	117 (17.1)
HBeAg-negative ALT ≥2.5 x ULN	112 (16.3)	108 (15.7)	113 (16.4)	111 (16.3)	113 (16.5)	118 (17.3)
Total N per population	687 (100)	659 (95.9)	687 (100)	680 (99.6)	655 (95.9)	680 (99.6)

Note: ITT population stratification based on IVRS; EE and Safety population stratification based on the last available laboratory value during Screening.
Source: Table 14.1.1

Source: Table 11-4, NV-02B-007 Study Report

Medical Officer Comments: *A total of 62 patients were assigned to the wrong stratum because the incorrect HBeAg status (28 patients) or ALT level (33 patients) or both (1 patient). Incorrect patient data was entered in error into the interactive voice response system (IVRS). For the primary endpoint, the primary efficacy analysis was reviewed based the correct HBeAg status (i.e. as determined by laboratory value upon screening) and based on the IVRS stratum assignment.*

HBV History and Baseline Disease Characteristics

Among HBeAg-positive patients in the ITT population, the majority (79%) had been diagnosed with HBV for more than one year. However, approximately 8% HBeAg-positive patients had been diagnosed with HBV within 6 months prior to study entry. The mean duration of HBV overall in this population was 6.1 ± 0.21 years. Most patients in this sub-group had had no prior interferon therapy (94% overall); while 6% had received prior interferon, most of whom were considered treatment failures.

Among HBeAg-negative patients in the ITT population, most patients had been diagnosed more than 1 year prior to study entry, and approximately 3% patients had been diagnosed in less than 6 months prior to study entry. Mean duration since first HBV diagnosis was longer in the HBeAg-negative group, approximately 9 years in comparison to approximately 6 years in the HBeAg-positive group. The majority of patients in this population had not received prior interferon therapy for HBV. These data are summarized by treatment group in the following table.

Table 12. HBV History in ITT Population by HBeAg Status

Parameter	HBeAg-positive			HBeAg-negative		
	Lamivudine N=463	Telbivudine N=458	Total N=921	Lamivudine N=224	Telbivudine N=222	Total N=446
Time since HBV diagnosis, n (%):						
> 1 year prior	363 (78.4)	365 (79.7)	728 (79.0)	195 (87.1)	206 (92.8)	401 (89.9)
> 6 months to 1 year	65 (14.0)	53 (11.6)	118 (12.8)	21 (9.4)	11 (5.0)	32 (7.2)
≤ 6 months	35 (7.6)	40 (8.7)	75 (8.1)	8 (3.6)	4 (1.8)	12 (2.7)
Data missing	--	--	--	0	1 (0.5)	1 (0.2)
Duration since first diagnosis, years:						
Mean (SD)	6.2 (0.29)	6.0 (0.31)	6.1 (0.21)	8.7 (0.5)	9.2 (0.37)	9.0 (0.37)
Range	0.3, 34.0	0.3, 35.0	0.3, 35.0	0.3, 37.0	0.3, 49.0	0.3, 49
Prior interferon therapy:						
No	431 (93.1)	436 (95.2)	867 (94.1)	200 (89.3)	196 (88.3)	396 (88.8)
Yes	32 (6.9)	22 (4.8)	54 (5.9)	24 (10.7)	26 (11.7)	50 (11.2)

Source: Tables 11-8 and 11-9, Study NV-02B-007 Study Report

Medical Officer Comments: *Among HBeAg-positive patients, the treatment groups were fairly well-balanced; however, more patients in the lamivudine group were diagnosed with HBV between 6 months and 1 year prior to study entry, although the mean duration since diagnosis was similar for the lamivudine and telbivudine groups. Numerically, more patients in the lamivudine 32/463 (6.9%) than in the telbivudine 22 (4.8%) treatment group had received prior interferon therapy for HBV. The majority of patients in both groups who had received prior interferon were considered previous treatment failures. In the HBeAg-negative subgroup, there were minor imbalances in time since diagnosis, but the majority in both treatment groups had been diagnosed with HBV for > 1 year. No statistically significant difference was noted between treatment groups with regards to HBV medical history for HBeAg-positive or –negative patients.*

Patients who had received any interferon during the year prior to study entry were excluded from the study.

Table 13. HBV Disease Characteristics at Baseline in ITT population

Characteristic	Lamivudine HBeAg-positive N=463	Telbivudine HBeAg-positive N=458	Lamivudine HBeAg-negative N-224	Telbivudine HBeAg-negative N=222
Mean HBV DNA (log10 copies/mL) (SE)[a]	9.53 (0.092)	9.51 (0.085)	7.42 (0.102)	7.54 (0.078)
Mean ALT (IU/L) (SE)[b]	158.9 (6.30)	146.2 (5.36)	143.7 (8.74)	137.0 (6.94)
Knodell necroinflammatory score (HAI score)[c]	7.3	7.4	7.6	7.3
Knodell fibrosis score	1.6	1.5	1.9	1.7
Ishak fibrosis score	2.2	2.1	2.5	2.3
HBeAg-positive	442 (95%)	432 (94)	4 (2)	8 (4)
HBeAb-positive	21 (5)	26 (6)	220 (98%)	215 (97)

[a] Source: Applicant's Tables 11-10 and 11-11 Study Report
[b] Source: Applicant's Tables 11-13 and 11-14
[c] Source: Applicant's Table 11-17 Study Report, Baseline histology scores in mITT population; for lamivudine HBeAg-positive, N=433; HBeAg-negative, N=218); for telbivudine HBeAg-positive, N=439; HBeAg-negative, N=212.

Medical Officer Comments: *Note that mean HBV DNA levels and ALT levels at baseline were somewhat higher among HBeAg-positive patients than HBeAg-negative patients in both treatment groups.*

HBV Genotypes at Baseline

The predominant HBV genotypes at baseline were genotypes B (26%) and C (51%); while genotypes A and D represented 6% and 16% of the overall study population, respectively. Fourteen patients had genotypes E, F, or G at baseline, 1 patients had a mixed HBV genotype (G/A), and genotype was unknown in 1 patient. The distribution of genotypes between treatment groups was generally well balanced.

Medical Officer Comments: *The most common HBV genotype in North America is A; while genotypes B and C are frequent in Asia and Oceania. HBV genotype has been shown to affect*

response to treatment with lamivudine or interferon (Palumbo, 2007); but little is known about the effect of HBV genotype on treatment response with other approved antiviral agents.

Efficacy Outcomes

Primary Efficacy Endpoint Analysis: Therapeutic Response at week 52 was the primary efficacy endpoint. This was a composite endpoint requiring suppression of HBV DNA to < 5 $\log_{10}$ copies/mL plus either clearance of HBeAg or ALT normalization. In HBeAg-negative patients, Therapeutic Response (or Composite Serological Response) was defined as serum HBV DNA < 5 $\log_{10}$ copies/mL and ALT normalized.

Medical Officer Comments: *Note that the primary endpoint, Therapeutic Response was measured at week 52; while Therapeutic Response at Week 104 was considered a secondary endpoint.*

The primary endpoint in this study was Therapeutic Response, defined as serum HBV DNA < 5 $\log_{10}$ copies/mL and either HBeAg loss or ALT normalized in HBeAg-positive patients, and defined as HBV DNA < 5$\log_{10}$ copies/mL and ALT normalized in HBeAg-negative patients.

Therapeutic Response at Week 52 and 104 by HBeAG status is shown in the following table. The applicant concluded that telbivudine achieved superiority for Therapeutic Response in HBeAg-positive ITT population and non-inferiority in the HBeAg-negative population at week 52. At week 104, a statistically significant treatment difference was noted in favor of telbivudine in HBeAg-positive and HBeAg-negative populations.

Table 14. Therapeutic Response in ITT Population

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

Medical Officer Comments*: This analysis was based on the applicant's IVRS method for stratification based on HBeAg status, and was confirmed by the Medical Officer from the datasets submitted with Study 007. In this analysis, telbivudine was found to be non-inferior to lamivudine at both Week 52 and Week 104 with respect to the primary endpoint, based on a pre-specified non-inferiority margin of -15%. At week 52, telbivudine was shown to be superior to*

lamivudine for this endpoint only in the HBeAg-positive sub-population; while at week 104, telbivudine was also superior to lamivudine in the HBeAg-negative population for the Therapeutic Response endpoint.

In the Statistical Reviewer's analysis of efficacy at Week 104, using the correct (i.e. laboratory) HBeAg classification, Dr. Fraser Smith found similar proportions of patients with a Therapeutic Response compared to the applicant's analysis, as shown in the following table.

Table 15. Therapeutic Response at Week 104 based on laboratory HBeAg status at screening

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	95.68% CI*	p-value†
ITT population				
HBeAg-positive	216/455 (47.5)	280/445 (62.9)	8.9, 22.1	<0.001
HBeAg-negative	155/232 (66.8)	182/235 (77.5)	2.2, 18.9	0.010

Source: Statistical Reviewer's Analysis
*CI adjusted for multiple comparison to test treatment/antigen status interaction with an α level of 0.0432
†Treatment group differences controlled for randomization strata: difference between proportions for categorical variables

The statistical reviewer also analyzed the primary efficacy endpoint, Therapeutic Response, in the Efficacy Evaluable population, as shown in the following table.

Table 16. Therapeutic Response at Week 52 (primary efficacy endpoint) and Week 104 by treatment and HBeAg status in the Efficacy Evaluable Population.

Group	Lamivudine n/N (%)	Telbivudine n/N (%)	95.68% CI*	p-value†
Week 52				
HBeAg-positive	297/438 (67.6)	331/430 (77.1)	3.5, 15.4	0.0014
HBeAg-negative	178/221 (80.6)	171/225 (76.0)	-12.5, 3.3	0.2372
Week 104				
HBeAg-positive	228/438 (51.9)	293/430 (68.2)	9.7, 22.9	<0.0001
HBeAg-negative	161/221 (72.9)	182/225 (80.9)	-0.1, 16.0	0.0450

Source: Table 14.2.1.4 of the NV-02B-007 Clinical Study Report
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

Medical Officer Comments: *The efficacy analysis of the primary endpoint, Therapeutic Response in the secondary analysis population, the efficacy evaluable population allows us to draw similar conclusions regarding telbivudine as for the ITT population. However, in the EE population at week 104, telbivudine was non-inferior to lamivudine for the HBeAg-positive and –negative subpopulation, and was superior to lamivudine only in the HBeAg-positive subgroup.*

Therapeutic Response at week 104 by Randomization Strata
Subjects were also stratified by serum ALT level at baseline, because ALT may influence the rate of HBeAg loss and seroconversion. Therapeutic response at week 104 by randomization strata is shown in the following table:

Table 17. Therapeutic Response by Randomization Strata

Table 11-23 Therapeutic Response at Week 104 by treatment and randomization strata - ITT population

Stratification group	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	*P*-value*
HBeAg+/ALT <2.5 x ULN	93/217 (42.9)	125/212 (59.0)	6.8, 25.4	0.0007
HBeAg+/ALT ≥2.5 x ULN	130/246 (52.8)	165/246 (67.1)	5.7, 22.8	0.0011
HBeAg-/ALT <2.5 x ULN	70/112 (62.5)	84/111 (75.7)	1.2, 25.2	0.0315
HBeAg-/ALT ≥2.5 x ULN	78/112 (69.6)	88/111 (79.3)	-1.7, 21.0	0.0968

Note: Percentages, CIs, and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*Comparison of proportions between treatment groups, controlling for randomization strata.
Source: Tables 14.2.1.7 and 14.2.1.9

Medical Officer Comments: *Telbivudine was non-inferior to lamivudine in each of the randomization strata based on a -15% non-inferiority margin, and was superior to lamivudine in each stratum except HBeAg-negative/ALT ≥ 2.5 xULN.*

Secondary Efficacy Endpoints: The key secondary endpoint in the study, histological response, was defined as ≥ 2 point reduction in Knodell necroinflammatory score without a worsening in fibrosis score. Histological Response was measured at Week 52 only and not at Week 104. Other important secondary endpoints in this study are defined below.

Table 18. Definition of Other Important Secondary Endpoints (Virological, Biochemical and Serological) in Study NV-02B-007

Secondary Endpoint	Definition
HBV DNA negative by PCR	HBV DNA < 300 copies/mL*
ALT normalization	If ALT levels were > ULN at baseline, ALT WNL on 2 consecutive visits or at the last visit
HBeAg loss	Loss of detectable HBeAg if HBeAg was detected at baseline
HBeAg seroconversion	HBeAg loss with gain of detectable HBeAb

*Roche COBAS Amplicor Assay (LLOQ ≤ 300 copies/mL
ULN= upper limits normal
WNL= within normal limits

Medical Officer Comments: *Mean HBV DNA reduction from baseline (log_{10} copies/mL) was not a pre-specified secondary endpoint in this study, but was included in the approved TYZEKA labeling, and is reviewed here as well.*

Histologic Response

Histologic Response was the key secondary efficacy endpoint in this study; however, liver biopsies were not performed, and histologic response was not measured at Week 104. Dr. Charlene Brown reviewed outcomes for this endpoint previously in her clinical review of October, 2006. As shown previously by the clinical and statistical reviewers, at Week 52, a significantly greater proportion of HBeAg-positive patients treated with telbivudine in the mITT population (all subjects with evaluable pre-treatment liver histology slides) had a histological response at week 52 compared to those treated with lamivudine. Among HBeAg-negative patients, histological response in patients treated with telbivudine was non-inferior to that in lamivudine. Additionally, no significant difference in Ishak Fibrosis score in either HBeAg sub-population with baseline Ishak Fibrosis score of ≥ 3. These data are summarized in the following table.

Table 19. Histologic Response at Week 52

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

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

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

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

Source: Table 2 of finalized LdT Label, based on Statistical Reviewer Analysis.

Proportion of Subjects with HBV DNA negative by PCR

As shown in the following table, a significantly higher proportion of subjects who received telbivudine than lamivudine achieved undetectable serum HBV DNA by PCR (COBAS Amplicor PCR assay, LLOQ < 300 copies/mL) at weeks 52 and 104, regardless of HBeAg status.

Table 20. Proportion of Patients with PCR-negative HBV DNA

Table 11-34 Proportion of patients with PCR-negative HBV DNA (<300 copies/mL) at Weeks 52 and 104, by HBeAg status - ITT population

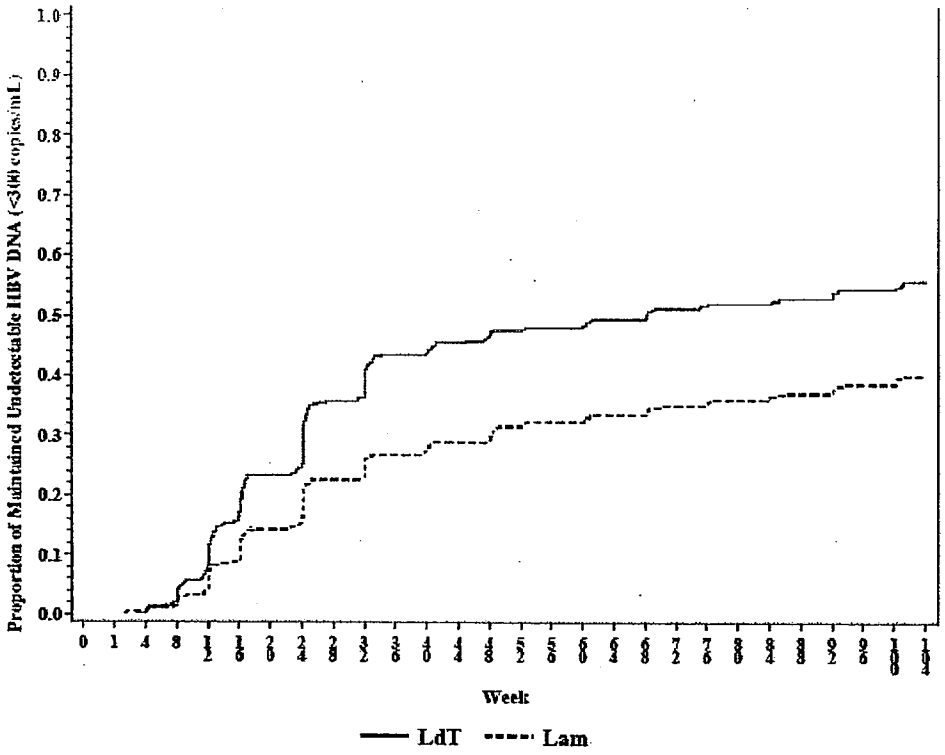
	HBeAg-positive			HBeAg-negative		
Time point	Lamivudine (N=463)	Telbivudine (N=458)	*P*-value*	Lamivudine (N=224)	Telbivudine (N=222)	*P*-value*
Week 52, n (%)	187 (40.4)	275 (60.0)	<0.0001	160 (71.4)	195 (87.8)	<0.0001
Week 104, n (%)	178 (38.5)	255 (55.6)	<0.0001	127 (56.7)	182 (82.0)	<0.0001

Note: Percentages and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*Comparison of proportions between treatment groups, controlling for randomization strata.
Source: Tables 14.2.1.3 and 14.2.1.5

Time to maintained PCR-undetectable HBV DNA (< 300 copies/mL) was shorter in telbivudine recipients than in subjects who received lamivudine as shown in the figures below. PCR-undetectable HBV DNA was maintained if HBV DNA was negative for at least 2 consecutive visits, and at the patient's last treatment visit, with no 2 intervening consecutive visits with PCR-positive HBV DNA.

Figure 2. Time to maintained PCR-undetectable HBV DNA (HBeAg-Positive Population)

Figure 11-7 Time to maintained PCR-negative HBV DNA (<300 copies/mL) - HBeAg-positive ITT population



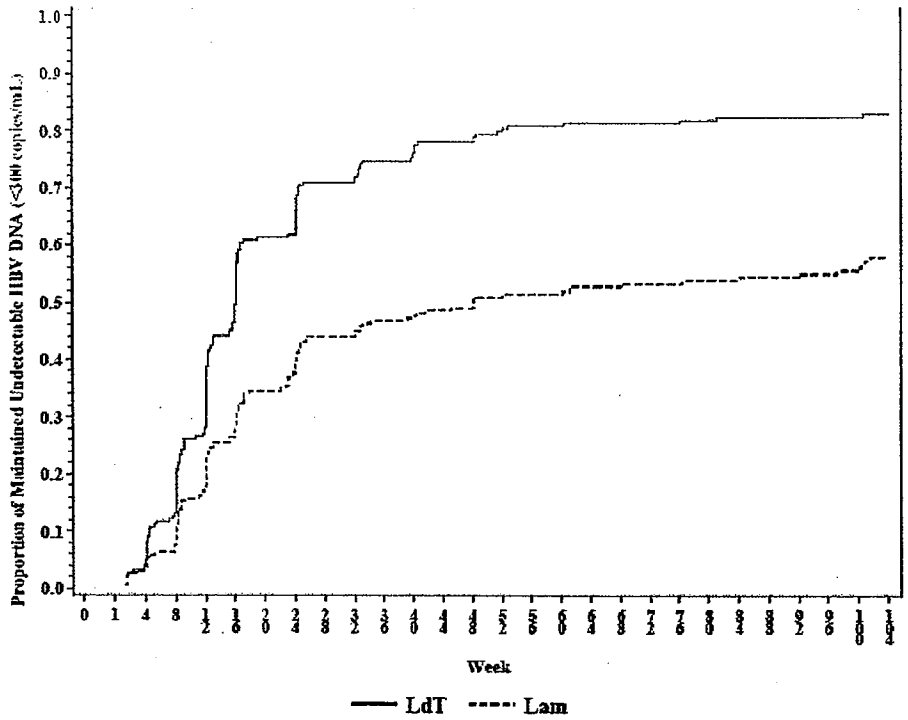
LdT = telbivudine, Lam = lamivudine

Note: Analysis censored at the earlier of Week 104, treatment discontinuation date (including due to efficacy), onset of on-treatment nonstudy HBV medication. Event time is Baseline to the starting time of the event.

Source: Figure 14.2.5.2, Table 14.2.11.5

Figure 3. Time to maintained PCR-undetectable HBV DNA (HBeAg-Negative Subpopulation)

Figure 11-8 Time to maintained PCR-negative HBV DNA (<300 copies/mL) - HBeAg-negative ITT population



LdT = telbivudine, Lam = lamivudine
Note: Analysis censored at the earlier of Week 104, treatment discontinuation date (including due to efficacy), or onset of on-treatment nonstudy HBV medication. Event time is Baseline to the starting time of the event.
Source: Figure 14.2.5.3, Table 14.2.11.6

Medical Officer's Comments: *The initial rate of HBV DNA suppression to undetectable levels was faster in the telbivudine than the lamivudine treatment group for both HBeAg sub-populations.*

ALT Normalization

ALT normalization was defined as normal serum ALT levels on 2 consecutive visits for a patient with elevated ALT (> 1.0 x ULN) at Baseline. The majority of patients in both treatment groups achieved ALT normalization by week 24. As summarized in the following table, in the HBeAg-positive sub-population, ALT normalization was observed in proportionally more telbivudine than lamivudine treated patients at weeks 76 and 104; while no difference was observed in this endpoint at weeks 24 or 52 in this population. In the HBeAg-negative sub-population, no significant difference was noted between treatment groups for ALT normalization in the HBeAg-negative sub-population at any timepoint.

Table 21. Proportion of Patients with ALT Normalization

Table 11-38 Proportion of patients with ALT normalization at Weeks 24, 52, 76, and 104 by HBeAg status - ITT population

	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	*P*-value*
HBeAg-positive				
Week 24, n (%)	299/446 (67.1)	289/440 (65.6)	-7.6, 4.6	0.6273
Week 52, n (%)	331/446 (74.3)	338/440 (76.8)	-3.1, 8.2	0.3776
Week 76, n (%)	306/446 (68.7)	330/440 (75.0)	0.4, 12.2	0.0351
Week 104, n (%)	275/446 (61.7)	306/440 (69.5)	1.6, 14.1	0.0135
HBeAg-negative				
Week 24, n (%)	**147/207 (71.0)**	**149/203 (73.4)**	**-6.3, 11.0**	**0.5978**
Week 52, n (%)	**161/207 (77.8)**	**148/203 (72.9)**	**-13.2, 3.4**	**0.2466**
Week 76, n (%)	**154/207 (74.4)**	**159/203 (78.3)**	**-4.3, 12.1**	**0.3554**
Week 104, n (%)	**145/207 (70.1)**	**158/203 (77.8)**	**-0.7, 16.2**	**0.0725**

Note: Percentages, CIs, and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*Comparison of proportions between treatment groups controlling for randomization strata. Patients with ALT ≤1 x ULN at Baseline excluded from analysis.
Source: Tables 14.2.1.3 and 14.2.1.5

HBeAg Loss and HBeAg Seroconversion

Among HBeAg-positive patients, loss of HBeAg without appearance of anti-HBe may denote decreased HBV replication and decreased HBV infectivity. Clearance of HBeAg, may reduce the risk of hepatic decompensation and improve survival, whether clearance is spontaneous or after antiviral therapy, as discussed by Lok and McMahon (2007). Seroconversion refers to loss of HBeAg and appearance of anti-HBe. Spontaneous seroconversion has been associated with low or undetectable HBV DNA, normal ALT and minimal or no necroinflammation on liver biopsy; while spontaneous reversion to HBeAg-positivity has been associated with reactivation of HBV replication and exacerbation of hepatitis (Lok and McMahon, 2007).

As shown in the following table, proportionately more patients in the telbivudine group achieved HBeAg loss and HBeAg seroconversion at both Week 52 and Week 104; however, the treatment difference was not statistically significant between treatment groups.

Table. 22. Proportion of Patients with HBeAg Loss and Seroconversion

Table 11-35 HBeAg loss and seroconversion at Weeks 24, 52, 76, and 104 - HBeAg-positive ITT population

	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	*P*-value*
HBeAg loss				
Week 24	65/442 (14.7)	69/432 (16.0)	−3.5, 6.0	0.5986
Week 52	103/442 (23.3)	111/432 (25.7)	−3.2, 8.1	0.4038
Week 76	126/442 (28.5)	141/432 (32.7)	−1.9, 10.2	0.1768
Week 104	129/442 (29.2)	152/432 (35.2)	−0.1, 12.2	0.0556
HBeAg seroconversion				
Week 24	59/442 (13.3)	65/432 (15.1)	−2.9, 6.3	0.4677
Week 52	95/442 (21.5)	97/432 (22.5)	−4.5, 6.4	0.7263
Week 76	108/442 (24.4)	116/432 (26.9)	−3.3, 8.2	0.4034
Week 104	109/442 (24.7)	128/432 (29.6)	−0.9, 10.8	0.0947

Note: Percentages and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*Comparison of proportions between treatment groups controlling for randomization strata.
Source: Table 14.2.1.3

Discontinuation of Treatment due to Efficacy

HBeAg-positive patients who achieved virologic response, HBeAg loss with HBV DNA < 5 $\log_{10}$ copies/mL were eligible for treatment discontinuation if they had completed at least 52 weeks of treatment and had undetectable HBV DNA for ≥ 24 weeks. HBeAg-negative patients were eligible for treatment discontinuation if they had achieved HBsAg loss at week 52 or subsequently on at least 2 consecutive visits.

a. Virologic Response in HBeAg-positive Sub-Population

The following table summarizes virologic response, HBeAg-loss with HBV DNA reduction to < 5 $\log_{10}$ copies/mL in the HBeAg subpopulation. Although the proportion of patients with virologic response was higher in telbivudine-treated patients, the differences between treatment groups were not statistically significant except at Week 104.

Table 23. Proportion of Patients with Virologic Response

Table 11-36 Proportion of patients with Virologic Response at Weeks 24, 52, 76, and 104 - HBeAg-positive ITT Population

Visit	Lamivudine n/N (%)	Telbivudine n/N (%)	95% CI	P-value*
Week 24	65/442 (14.7)	69/432 (16.0)	−3.5, 6.0	0.5986
Week 52	101/442 (22.8)	111/432 (25.7)	−2.8, 8.5	0.3197
Week 76	123/442 (27.8)	140/432 (32.4)	−1.4, 10.6	0.1337
Week 104	122/442 (27.6)	147/432 (34.0)	0.3, 12.5	0.0383

Note: Percentages, CIs, and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*Comparison of proportions between treatment groups controlling for randomization strata: ANOVA.
Source: Table 14.2.1.3

H

b. HBsAg loss

HBsAg loss was reported in a total of 6 HBeAg-positive patients in each treatment group by Week 104, and in 3 HBeAg-negative patients, 2 in the lamivudine treatment group and 1 in the telbivudine group by Week 52, with no change at Week 104.

c. Discontinuation due to Efficacy

The following table shows the numbers and proportions of patients who qualified for treatment discontinuation, and the proportions of patients who actually discontinued treatment due to efficacy. All patients who discontinued treatment were to remain on study to assess post-treatment durability of efficacy responses. By Week 104, approximately one-quarter of HBeAg-positive patients qualified for treatment discontinuation, but only 20-30% of those qualified, were actually discontinued from treatment Of those who discontinued treatment for efficacy, 2/20 (10%) patients in the lamivudine group, and 6/39 (15.4%) of those in the telbivudine group experienced a disease relapse, requiring treatment re-initiation. Among HbeAg-negative patients, only 7 patients (4 lamivudine and 3 telbivudine) qualified for treatment discontinuation by Week 104, and only 1 lamivudine-treated patient was discontinued, but no follow-up information on that patient was available.

Table 24. Discontinuation of Treatment due to Efficacy

Table 11-39 Proportion of patients who discontinued treatment for efficacy by Week 104 – ITT population

	HBeAg-positive		HBeAg-negative	
	Lamivudine (N=463) n (%)	Telbivudine (N=458) n (%)	Lamivudine (N=224) n (%)	Telbivudine (N=222) n (%)
Qualified for treatment discontinuation*, Week 52	39 (8.4)	44 (9.6)	4 (1.8)	2 (0.9)
Qualified for treatment discontinuation*, Week 76	81 (17.5)	93 (20.3)	4 (1.8)	3 (1.4)
Qualified for treatment discontinuation*, Week 104	102 (22.0)	119 (26.0)	4 (1.8)	3 (1.4)
Discontinuations for efficacy	20 (4.3)	39 (8.5)	1 (0.4)	0
Disease relapsed	2/20 (10.0)	6/39 (15.4)	0†	0
Treatment restarted	3/20 (15.0)	6/39 (15.4)	0†	0

*Based on investigator assessment.
†Follow-up data are unavailable for the patient who discontinued due to efficacy (Table 14.2.22.3).
Source: Tables 14.2.17.3 and 14.2.17.5

Medical Officer Comments: *The criteria used in this study for treatment discontinuation for efficacy differ from the most recent AASLD guidelines which state that nucleoside treatment for chronic HBV may be stopped in HBeAg-positive patients with HBeAg seroconversion who have completed at least 6 months of additional treatment; and in HBeAg-negative patients who have confirmed HBsAg loss (Lok and McMahon, 2007).*

The applicant also analyzed durability of treatment response based on several efficacy endpoints in patients who discontinued treatment due to efficacy compared to those who were eligible for discontinuation, but continued therapy. A higher proportion of patients who continued on treatment maintained HBV DNA suppression, HBeAg seroconversion, and ALT normalization, particularly in the telbivudine treatment group. These data are summarized in the following table.

Table 25. Durability of Treatment Response in Patients who met criteria for Treatment Discontinuation due to Efficacy by Week 104

Table 11-40 Durability of efficacy responses in patients who qualified for treatment discontinuation due to efficacy by Week 104 - HBeAg-positive ITT population

	Lamivudine (N=463)	Telbivudine (N=458)
Efficacy Response	**n/N (%)**	**n/N (%)**
Patients who discontinued treatment*	20/102 (20)	39/119 (33)
Sustained Virologic Response	14/19 (74)	18/38 (47)
Sustained HBeAg loss	17/19 (89)	31/38 (82)
Sustained HBeAg seroconversion	15/17 (88)	28/35 (80)
Sustained HBV DNA suppression (<5 $\log_{10}$ copies/mL)	14/18 (78)	18/38 (47)
Sustained ALT normalization (≤1 x ULN)	11/16 (69)	21/33 (64)
Patients who did not discontinue treatment†	82/102 (80)	80/119 (67)
Maintained Virologic Response	68/82 (83)	68/80 (85)
Maintained HBeAg Loss	68/82 (83)	69/80 (86)
Maintained HBeAg seroconversion	61/82 (74)	60/80 (75)
Maintained HBV DNA Suppression (<5 $\log_{10}$ copies/mL)	73/82 (89)	71/80 (89)
Maintained ALT Normalization (≤1 x ULN)	73/82 (89)	69/80 (86)

*Numerators include patients who sustained a response through the last post-treatment visit; denominators include patients who qualified for treatment discontinuation and maintained the response through treatment discontinuation and had at least one post-treatment visit.
†Numerators include patients who maintained a response through the last available on-study visit.
Source: Table 14.2.18.3

Mean HBV DNA Reduction from Baseline

At Week 104, mean HBV DNA reduction from baseline was somewhat less in comparison to that observed at Week 52 in both treatment groups. Mean HBV DNA reduction from baseline was greater in the telbivudine treatment arm than the lamivudine arm at both time points and in both HBeAg sub-populations.

Table 26. Mean HBV DNA Reduction from Baseline in the ITT Population

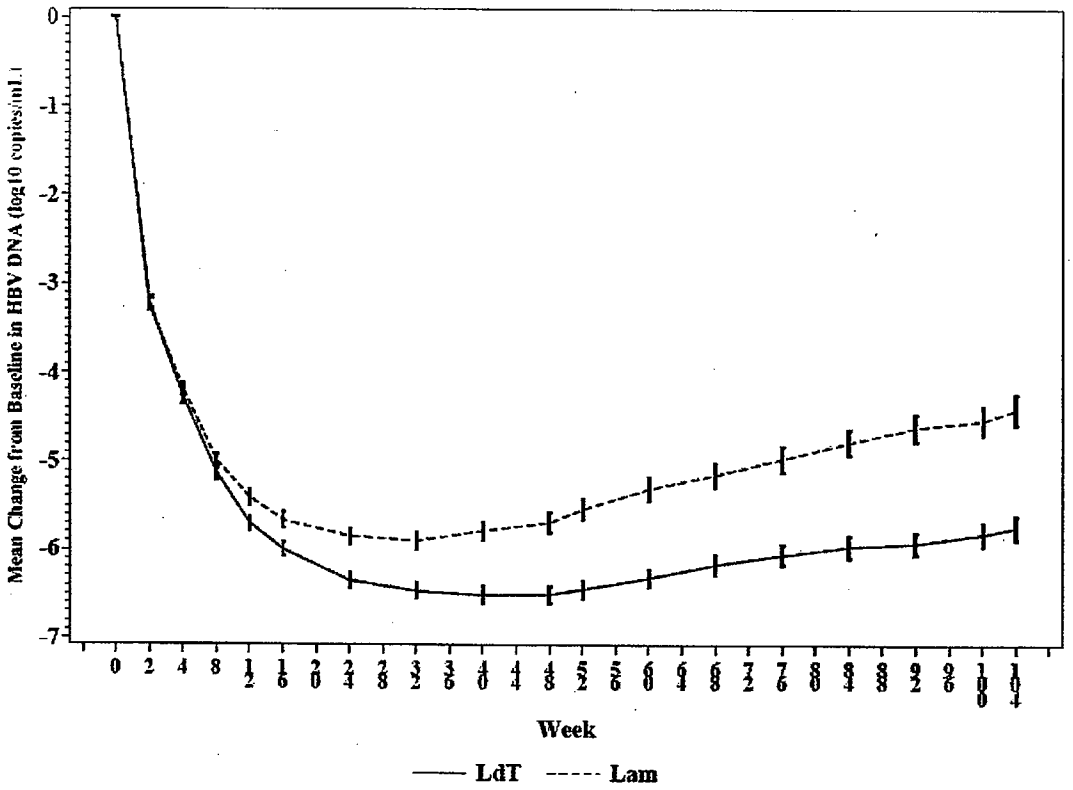
Mean HBV DNA Reduction from Baseline (log10 copies/mL) ± SE	HBeAg-Positive		HBeAg-Negative	
	Telbivudine	Lamivudine	Telbivudine	Lamivudine
Time Point				
Week 52	-6.45 ± 0.11 N= 443	-5.55 ±0.11 N=443	-5.22 ± 0.13 N=219	-4.40 ± 0.13 N=218
Week 104	-5.74 ± 0.15 N=398	-4.42 ± 0.15 N=387	-5.00 ± 0.15 N=208	-4.17 ± 0.16 N=189

Source: Table 11-13 Study Report
SE= standard error

The applicant analyzed mean change in HBV DNA from baseline to Week 104 for both HBeAg sub-populations as shown in the following two figures. In the HBeAg-positive sub-population, the mean change in HBV DNA from baseline was significantly greater in the telbivudine at each time point measured from Week 12 through Week 104; while in the HBeAg-negative sub-population, the mean change DNA from baseline was significantly greater in the telbivudine at each time point measured from Week 8 through Week 104.

Figure 4. Mean Change HBV DNA levels from Baseline to Week 104 (HBeAg-Positive)

Figure 11-5 Mean change (+/−SE) from Baseline to Week 104 in HBV DNA levels by visit – HBeAg-positive ITT population



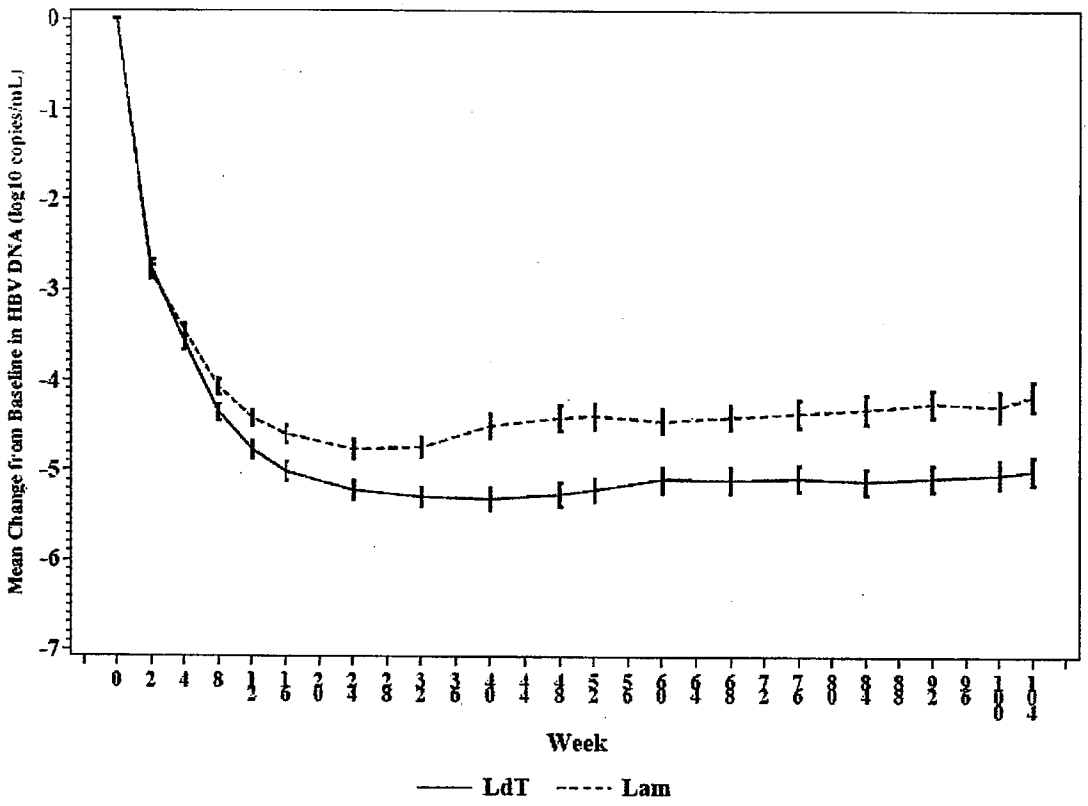
LdT = telbivudine, Lam = lamivudine

Note: Observations after treatment discontinuation due to efficacy or after onset of nonstudy anti-HBV medications are excluded.

Source: Figure 11-5 Study Report

Figure 5. Mean Change HBV DNA levels from Baseline to Week 104 (HBeAg-Negative)

Figure 11-6 Mean change (+/−SE) from Baseline to Week 104 in HBV DNA levels by visit – HBeAg-negative ITT population



LdT = telbivudine, Lam = lamivudine

Note: Observations after treatment discontinuation due to efficacy or after onset of nonstudy anti-HBV medications are excluded.

Source: Figure 11-6 Study NV-02B-007 Study Report

Medical Officer Comments: *These figures show mean HBV DNA reduction over time differed between treatment groups, starting at approximately weeks 8-12 of treatment.*

Virologic Breakthrough

Protocol-defined virologic breakthrough included two definitions applicable to patients who met the entry criterion of baseline serum HBV ≥ 6 $\log_{10}$ copies/mL. Protocol-defined virologic breakthrough was defined as follows:

1. While on treatment, the patient achieved HBV DNA <5 $\log_{10}$ copies/mL on 2 consecutive visits, and subsequently had HBV DNA ≥ 5 $\log_{10}$ copies/mL on 2 consecutive visits with no more than one subsequent HBV DNA value <5 $\log_{10}$ copies/mL. The patient's HBV DNA at the last treatment visit must also have been ≥ 5

$\log_{10}$ copies/mL. If a patient had a single qualifying HBV DNA value (≥ 5 $\log_{10}$ copies/mL) at the last treatment visit, this result also qualified as a Virologic Breakthrough.

2. While on treatment, the patient did not achieve at least 2 consecutive HBV DNA values <5 $\log_{10}$ copies/mL but achieved a decrease in serum HBV DNA of at least 2 $\log_{10}$ copies/mL from Baseline on 2 consecutive visits. If serum HBV DNA returned to within 1 $\log_{10}$ copies/mL of Baseline on 2 consecutive visits, with no more than one subsequent value >1 $\log_{10}$ copies/mL below Baseline through the last treatment visit, the result qualified as Virologic Breakthrough. If such a patient's serum HBV DNA returned to within 1 $\log_{10}$ copies/mL of Baseline only at the last treatment visit, this result also qualified as a Virologic Breakthrough by this definition.

Subsequently, the applicant updated the definition of virologic breakthrough to be consistent with the most recent AASLD definition (Lok and McMahon, 2007). The updated definition of virologic breakthrough was called "1 log above nadir" breakthrough is a confirmed increase of ≥ 1 $\log_{10}$ copies/mL above nadir HBV DNA in those patients with a confirmed treatment response (i.e. ≥ 1 $\log_{10}$ reduction in HBV DNA below baseline HBV DNA level at 2 or more consecutive visits). The following table summarized virologic breakthrough using the protocol-defined definition for this endpoint and the updated definition as described above. More lamivudine- than telbivudine-treated patients experienced virologic breakthrough at Week 52 and Week 104 using either definition and regardless of HBeAg status at baseline.

Table 27. Virologic Breakthrough at Weeks 48 and 104

Table 11-41 Virologic breakthrough at Weeks 48 and 104, by HBeAg status - ITT population

	HBeAg-positive			HBeAg-negative		
	Lamivudine	Telbivudine	*P*-value*	Lamivudine	Telbivudine	*P*-value*
Endpoint	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Week 48						
Protocol-defined Virologic Breakthrough	46/442 (10.4)	15/438 (3.4)	<0.0001	16/187 (8.5)	4/192 (2.1)	0.0052
"1 log above nadir" Virologic Breakthrough"	71/463 (15.3)	27/458 (5.9)	<0.0001	28/224 (12.5)	5/222 (2.3)	<0.0001
Week 104						
Protocol-defined Virologic Breakthrough	164/442 (37.1)	102/438 (23.3)	<0.0001	37/187 (19.7)	16/192 (8.4)	0.0013
"1 log above nadir" Virologic Breakthrough"	211/463 (45.5)	131/458 (28.6)	<0.0001	68/224 (30.4)	27/222 (12.2)	<0.0001

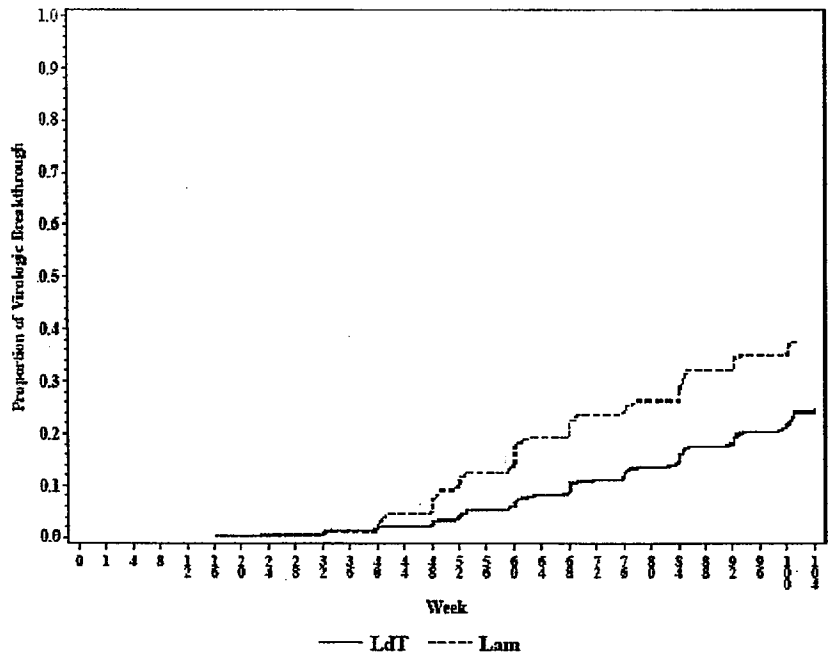
Note: Percentages and *P*-values calculated using Mantel-Haenszel weighted estimates based on randomization strata.
*Comparison of proportions between treatment groups controlling for randomization strata: ANOVA.
Source: Tables 14.2.1.3 and 14.2.1.5; Listing 16.2.6.7

Medical Officer Comments: *The "1 log above nadir" virologic breakthrough endpoint captured more breakthroughs than the protocol defined endpoint.*

Time to virologic breakthrough (protocol-defined) was more rapid among lamivudine than telbivudine-treated patients, as depicted in the following figures.

Figure 6. Time to Protocol-Defined Virologic Breakthrough (HBeAg-positive)

Figure 11-11 Time to protocol-defined Virologic Breakthrough – HBeAg-positive ITT population



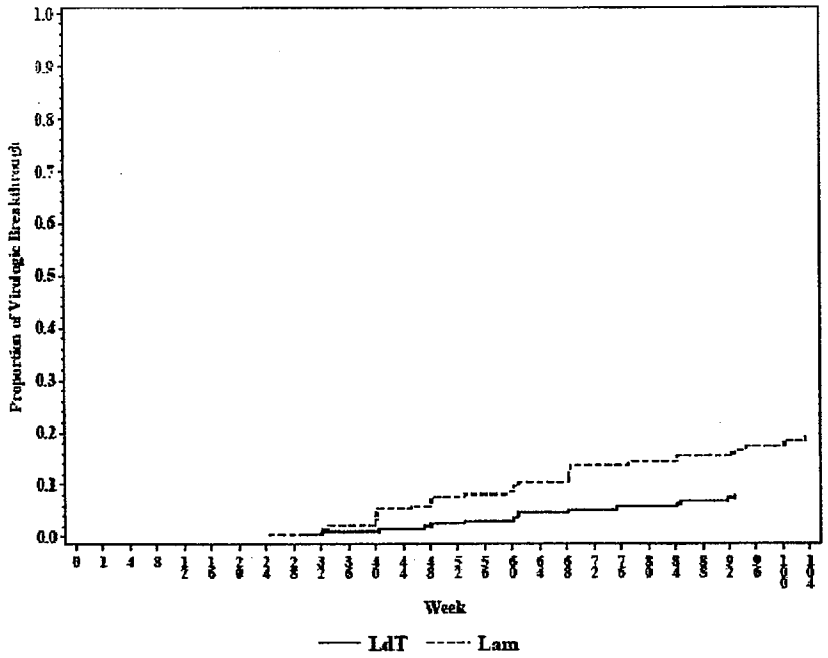
LdT = telbivudine; Lam = lamivudine

Note: Analysis censored at the earlier date of Week 104, treatment discontinuation for efficacy, or onset of nonstudy HBV medication.

Source: Figure 14.2.15.2, Table 14.2.19.2

Figure 7. Time to Protocol-Defined Virologic Breakthrough (HBeAg-negative)

Figure 11-12 Time to protocol-defined Virologic Breakthrough – HBeAg-negative ITT population



LdT = telbivudine; Lam = lamivudine
Note: Analysis censored at the earlier date of Week 104, treatment discontinuation for efficacy, or onset of nonstudy HBV medication.
Source: Figure 14.2.15.3, Table 14.2.19.3

Subgroup Analysis

Therapeutic Response by Gender

In the ITT population, there were a total of 1035/1367 (75.7%) males and 332/1367 (24.3%) females. The sponsor's analysis of the primary endpoint, Therapeutic Response by gender is shown in the following table.

Table 28 .Therapeutic Response at week 104 in ITT population by Gender

Gender	Lamivudine n/N(%)	Telbivudine n/N(%)	Treatment Difference (%)	95% Confidence Interval
HBeAg-positive				
Male	167/351 (47.6)	200/333 (60.1)	12.5%	(5.2, 19.9)
Female	56/112 (50)	90/125 (72.1)	22.1 %	(9.9, 34.2)
HBeAg-negative				
Male	114/177 (64.5)	137/174 (78.7)	14.2%	(4.9, 23.5)
Female	34/47 (72.2)	35/48 (72.7)	0.5%	(-17.5, 18.5)

Source: applicant's tables 14.2.1.15

Medical Officer Comments: *Telbivudine was superior to lamivudine for this endpoint in HBeAg-positive males and females; and in HBeAg-negative males. Therapeutic Response was proportionately higher in telbivudine-treated females than males in the HBeAg-positive subpopulation; but this pattern was not observed in the HBeAg-negative stratum.*

Therapeutic Response by Age

In the ITT population, there were 494/1367 (36.1%) patients < 30 years old, 686/1367 (50.2%) between 30-50 years old, and 187/1367 (13.7%) > 50 years old. The sponsor's subset analysis of therapeutic response by age group is shown in the following table.

Table 29.Therapeutic Response at week 104 in ITT population by Age Group

Age Group	Lamivudine n/N(%)	Telbivudine n/N(%)	Treatment Difference (%)	95% Confidence Interval
Overall Population*				
< 30 years old	125/238 (52.1)	184/256 (72.2)	20.1%	(11.9, 28.3)
30-50 years	187/349 (53.7%)	224/337 (66.2)	12.5%	(5.4, 19.7)
> 50 years	59/100 (61.2)	54/87 (62.8)	1.6%	(-12.8, 16.0)
HBeAg-positive				
< 30 years old	100/208 (47.6)	154/224 (69.1)	21.5%	(12.4, 30.5)
30-50 years	105/214 (49.2)	116/205 (56.3)	7.1%	(-2.5, 16.6)
> 50 years	18/41 (46.3)	20/29 (70.3)	24.0%	(0.5, 47.5)
HBeAg-negative				
< 30 years old	25/30 (83.2)	30/32 (93.8)	1.6%	(-5.1, 26.3)
30-50 years	82/135 (60.7)	108/132 (81.8)	21.1%	(10.6, 31.6)
> 50 years	41/59 (69.5)	34/58 (58.7)	-10.9%	(-28.1, 6.4)

*HBeAg-positive and HBeAg-negative
Source: Tables 14.2.1.11, 14.2.3.7, 14.2.3.8 Study Report, NV-02B-007

Medical Officer Comments: *The applicant did not provide a rationale for the age grouping used in this analysis. Although limited by small numbers of patients > 50 years old, this analysis suggests that telbivudine is superior to lamivudine in patients < 50 years old, and non-inferior in patients > 50 years old in the overall population. However, when HBeAg status is taken into account, telbivudine is superior to lamivudine for HBeAg-positive patients < 30 or > 50 years old, and in HBeAg-negative patients between the ages of 30 and 50 years. Within the telbivudine treatment group in the overall population, the proportion of patients with therapeutic response decreased with age. This pattern did not hold, however for the HBeAg subpopulations. Interpretation of these data is limited by analysis of subsets within subpopulations.*

Therapeutic Response by Race

Race/ethnicity was classified by the sponsor as Asian (1040/1367, 76.1%), Caucasian (209/1367, 15.3%), and "Other" (116/1367, 8.6%). The sponsor's subset analysis for therapeutic response by race/ethnic group in the ITT population is shown in the following table.

Table 30. Therapeutic Response at week 104 in ITT population by Race/Ethnic Group (adapted from tables 11.43 and 11.44 in study report)

Race/Ethnic Group	Lamivudine n/N(%)	Telbivudine n/N(%)	Treatment Difference (%)	95% Confidence Interval
HBeAg-positive:				
Asian	182/371 (49.1)	245/380 (64.5)	15.4%	(8.4, 22.4)
Caucasian	27/55 (49.6)	32/52 (61.1)	11.5%	(-7.1, 30.0)
Other	14/37 (38.3)	13/26 (50.0)	11.7%	(-13.4, 36.8)
HBeAg-negative				
Asian	103/144 (71.7)	118/145 (81.3)	9.6%	(-0.1, 19.3)
Caucasian	34/56 (60.6)	32/46 (69.3)	8.7%	(-9.9, 27.3)
Other	11/24 (45.8)	22/31 (71.0)	25.2%	(-0.3, 50.6)

Medical Officer Comments: *The point estimates for therapeutic response in telbivudine-treated subjects were higher than that in lamivudine-treated subjects regardless of racial/ethnic origin. In HBeAg-positive or –negative patients treated with telbivudine, therapeutic response was higher in the Asian subset than in other racial/ethnic groups. Telbivudine was non-inferior to lamivudine within each of the subsets; however, telbivudine was superior to lamivudine only in the HBeAg-positive subjects of Asian origin. Within the telbivudine subgroups, the highest rate of Therapeutic Response was observed in Asian patients; however, the subgroups of Caucasian and "other" races are much smaller in comparison.*

Therapeutic Response by Geographic Location

Recruitment of subjects into the ITT population by geographic region was 998/1367 (73%) from Asia, 164/1367 (12%) from North America, and 205/1367 (15%) from "other" locations (Europe, New Zealand and Australia).

Table 31. Therapeutic Response at week 104 in ITT population by Geographic Region

Geographic Region	Lamivudine n/N(%)	Telbivudine n/N(%)	Treatment Difference (%)	95% Confidence Interval
HBeAg-positive:				
Asia	176/350 (50.3)	235/355 (66.2)	16.0%	(8.8, 23.1)
North America	22/59 (37.6)	23/48 (47.7)	10.1%	(-8.7, 28.8)
"Other"	25/54 (46.3)	32/55 (58.1)	11.8	(-6.8, 30.4)
HBeAg-negative:				
Asia	93/139 (67.2)	122/154 (78.9)	11.7%	(1.6, 21.8)
North America	22/31 (68.8%)	19.26 (73.8%)	5.0%	(-19.0, 28.9)
"Other"	33/54 (61.3)	31/42 (72.8%)	11/5%	(-7.3, 30.2)

Source: Tables 14.2.1.24 and 14.2.1.25, NV-02B-007 Study Report

Medical Officer Comments: *The point estimates for the treatment difference between telbivudine and lamivudine favored telbivudine in each of these subsets. In Asian patients, telbivudine was non-inferior (and superior) to lamivudine in HBeAg-positive and-negative subjects using a -15% non-inferiority margin. With the exception of North American HBeAg-negative subjects, telbivudine was non-inferior to lamivudine. In HBeAg-positive subjects, therapeutic response rates were relatively low in North American subjects and in those from other regions in comparison to Asian subjects. However, these data are limited by the small numbers of subjects enrolled in North America and "other" regions, as well as by subset analysis. Only limited conclusions can be drawn from these subgroup analyses due to the limited number of non-Asian patients, patients older than 50 years old, and females.*

The applicant performed a number of other subset analyses for the primary endpoint, therapeutic response, and found that telbivudine was non-inferior to lamivudine in HBeAg-positive patients regardless of ALT baseline level. In the HBeAg-negative subpopulation, however, telbivudine was non-inferior to lamivudine only in patients with baseline ALT < 5 x ULN. When Therapeutic Response was analyzed by baseline HBV DNA level, telbivudine was found to be non-inferior to lamivudine regardless of baseline HBV DNA level (< 7, 7 to 9, or > 9 $\log_{10}$ copies/mL). Within the telbivudine treatment group, therapeutic response was somewhat higher among patients with lower baseline HBV DNA. Analysis of therapeutic response by baseline HBV genotype showed that telbivudine was non-inferior to lamivudine for patients HBV genotypes B, C, and D in the HBeAg-positive sub-population, and for HBV genotypes A, B, C, and D in the HBeAg-negative sub-population.

Medical Officer Comments: These subset analyses should be considered exploratory.

Outcome by Baseline HBV Genotype

Table 32. Therapeutic Response at week 104 in ITT population by HBV Genotype

HBV Genotype	Lamivudine n/N(%)	Telbivudine n/N(%)
HBeAg-positive:		
HBV genotype A	13/31 (39.2)	11/24 (46.8)
HBV genotype B	56/113 (49.5)	76/129 (59.1)
HBV genotype C	128/258 (49.8)	172/259 (66.3)
HBV genotype D	22/54 (40.5)	30/42 (71.3)
Other	4/7 (54.1%)	¼ (41.0)
HbeAg-negative:		
HBV genotype A	7/14 (50)	10/12 (83.6)
HBV genotype B	39/59 (66.1)	47/59 (79.7)
HBV genotype C	64/86 (74.6)	72/89 (80.7)
HBV genotype D	38/64 (59.3)	41/57 (72.1)
Other	0/1 (0)	2/4 (33.3)

Source: Tables 11-46, 11-47, 14.2.1.21, and 14.2.1.22 Study Report

Medical Officer Comments: *Because most of these subgroups are small, meaningful conclusions regarding effect of baseline HBV genotype on the primary endpoint, Therapeutic Response are limited. Among patients treated with telbivudine, the highest responses were achieved in those with genotypes B, C, and D regardless of HBeAg status.*

Discussion of Efficacy Findings in Study 007

Study NV-02B-007 provided substantial evidence of efficacy for telbivudine in the treatment of chronic hepatitis B in adults. The primary endpoint, Therapeutic Response (HBV DNA < 5 $\log_{10}$ copies/mL and either ALT normalization or HBeAg loss) at week 52 was reported in 75% telbivudine and 67% lamivudine HBeAg-positive patients, and in 75% telbivudine and 77% lamivudine HBeAg-negative patients as reviewed for the original NDA 22-011 by Dr. Charlene Brown. Histological response, the key secondary endpoint, measured at week 52, was reported in 69% telbivudine and 60% lamivudine HBeAg-positive patients, and in 69% telbivudine and 68% lamivudine HBeAg-negative patients. At 104 weeks, telbivudine was both non-inferior (and superior) to lamivudine in both HBeAg-positive and –negative patients based on Therapeutic Response in the ITT population. Histological response was not measured at week 104 in this study. Other important secondary endpoints also favored treatment with telbivudine over lamivudine at week 104, including mean HBV reduction from baseline, proportion of patients with undetectable HBV DNA by PCR, and HBeAg loss and seroconversion measured at week 104; while ALT normalization was similar in both treatment arms. Several limitations to this study included the low numbers of African American and Hispanic patients in the study, a predominantly Asian and male study population, and lack of histological characterization at week 104. Additionally, for patients enrolled in Study 007 who did not enroll in the follow-on Study, 022, follow-up for relapse was only for 4 months post-treatment. A higher proportion of patients treated with lamivudine than with telbivudine experienced virologic breakthrough by

week 104 in this study. Only limited conclusions can be drawn from the subgroup analyses of efficacy.

Outcome of Safety Assessments

Demographics of Safety Population

The safety population in this study was the ITT population, all randomized patients who received at least one dose of study drug and who had at least one observation after baseline. Patient demographics in the ITT population was shown in Table 9 above.

Extent of Exposure

Patients in this study received either 600 mg telbivudine daily or 100 mg lamivudine daily, and no dose modifications were permitted on study. Mean and median duration of exposure was similar in the two treatment groups as shown in the following table. In the applicant's analysis, overall exposure was similar in the HBeAg-positive and –negative subpopulations.

Table 33. Overall Treatment Exposure

Table 12-2 Overall treatment exposure - overall Safety population

Exposure (weeks*)	Lamivudine (N=687)	Telbivudine (N=680)
Mean (SE)	99.3 (0.68)	100.2 (0.62)
Median	104.1	104.1
25%, 75%	103.9, 105.0	103.9, 105.0
Range	1-127	2-127

*Number of weeks from Baseline to the last visit date on study, the last dose date for patients who discontinued study early, and the day before treatment discontinuation for patients who discontinued due to efficacy

The following table further describes duration of treatment in this study.

Table 34. Duration of Treatment in ITT Population

Duration of Treatment (weeks)	Lamivudine N=687 n/N (%)	Telbivudine N=680 n/N (%)
< 24 weeks	11 (1.6)	8 (1.2)
≥ 24 to < 52 weeks	12 (1.7)	7 (1.0)
≥ 52 to < 104 weeks	173 (25.2)	156 (23)
≥ 104 weeks	491 (71.5)	509 (74.9)

Source: Table 14.1.5.1.1 Study Report

Medical Officer Comments: *Although 70-75% patients in both treatment groups received at least 104 weeks of treatment, approximately 25% patients in each group received < 104 weeks. In some cases, exposure may have been longer than 104 weeks in this study because telbivudine was continued until patients were enrolled in the follow-on study NV-02B-022, an open label study to assess longer term safety of telbivudine.*

Safety Assessments
Safety was assessed by collection of all adverse events, and serious adverse events, with assessment of severity and relationship to study drug. Safety laboratory monitoring included hematology, and serum chemistry, and urinalysis. Physical examinations and vitals signs were also monitored. ECGs were not performed in this study. For analysis of safety data, 3 treatment periods were defined:

- **On Treatment:** from baseline to date of last treatment plus 7 days, and from restarting study medication to 7 days after the date of last treatment
- **Off Treatment:** 8 days after the date of last treatment to date of study discontinuation, or date of restarting therapy, whichever was applicable. The off-treatment analyses were only for patients who discontinued treatment due to efficacy during the study.
- **Post Treatment:** 8 days after the date of last treatment to date of study discontinuation through the follow-up period of the study, primarily for patients who prematurely discontinued the study or elected not to enter the follow-on study NV-02B-022 after completion of NV-02B-007.

Medical Officer Comments: *Patients who discontinued the study prematurely and those who completed the study did not enter the follow-up treatment study, NV-02B-022 were followed at months 1, 2, 3, and 4 off treatment.*

Overall Summary of Adverse Events in Study 007

Table 35. Summary of Adverse Events reported from Baseline to End-of-Study (ITT population)

Parameter	Lamivudine N=687	Telbivudine N=680
Patients with any adverse event	529 (77%)	551 (81)
Patients with any drug-related adverse event	159 (23.1)	197 (29.0)
Patients with Moderate-Severe adverse event	187 (27.2)	203 (29.9)
Patients with Serious Adverse Event	44 (6.4)	33 (4.9)
Deaths	1	0
Patients who discontinued treatment due to adverse event	26 (3.8)	27 (4.0)
Patients who discontinued treatment due to SAE	7 (1.0)	2 (0.3)

Deaths
One death, due to a fatal traffic accident was reported in Study 007 in a lamivudine-treated patient.

Medical Officer Comments: *The narrative for this patient was reviewed, and the reviewer agrees that the death was not likely related to study medication.*

Serious Adverse Events

Serious adverse events were reported in 44/687 (6.4%) lamivudine patients and 33/680 (4.9%) telbivudine patients from baseline to end of study, as shown in the following table.

Table 36 . Serious Adverse Events (on-treatment) from Baseline to End-of-Study by SOC

Serious Adverse Event SOC	Lamivudine N=687 n(%)	Telbivudine N=680 n(%)
Patients Reporting an SAE	44 (6.4)	33 (4.9)
Cardiac Disorders:	0	4 (0.6)
Congenital, familial and genetic disorders	0	1 (0.1)
Ear and labyrinth disorders	1 (0.1)	2 (0.3)
Endocrine disorders	1 (0.1)	0
Eye Disorders	0	1 (0.1)
Gastrointestinal disorders	4 (0.6)	2 (0.3)
General Disorders:	1	3 (0.4)
Hepatobiliary disorders:	1 (0.1)	3 (0.4)
Infections and Infestations:	15 (2.2)	6 (0.9)
Injury, poisoning, and procedural complications	6 (0.9)	8 (0.6)
Investigations:	3 (0.4)	2 (0.3)
Musculoskeletal and connective tissue disorders:	1 (0.1)	2 (0.3)
Neoplasms benign, malignant, unspecified	5 (0.7)	4 (0.6)
Nervous system disorders	3 (0.4)	1 (0.1)
Pregnancy, puerperium, and perinatal conditions	1 (0.1)	0
Psychiatric disorders	0	1 (0.1)
Renal and urinary disorders	2 (0.3)	3 (0.4)
Reproductive system and breast disorders	2 (0.3)	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	0
Vascular disorders	0	2 (0.3)

Source:

Medical Officer Comments: *Most serious adverse events were reported in the first year of the study in both treatment groups. On review of the A_AE dataset for this study, overall, 97 (53 lamivudine, 44 telbivudine) on-treatment serious adverse events were reported in the study, 63 (40 lamivudine, 23 telbivudine SAEs in the first year, and 34 (13 lamivudine and 21 telbivudine) in the second year. Overall 77 patients experienced on-treatment serious adverse events in the study (44 lamivudine, 33 telbivudine). Fifty three (53) patients (33 lamivudine, 20 telbivudine) experienced SAE in the first year of the study, and 27 patients (11 lamivudine and 16 telbivudine) experienced SAEs in the second year of the study. Three patients in the telbivudine group had SAEs in both the first and second year (included in above total). Seven additional*

patients (3 lamivudine, 4 telbivudine) experienced SAEs which were not considered treatment-emergent (all 4 in the telbivudine group were prior to treatment; while in the lamivudine group 1 was pre-treatment, 1 was off-treatment, and 1 was post-treatment).

Table 37. Serious Adverse Events in Telbivudine Treatment Group in Study 007

Site-patient ID	Event ID	Event (verbatim)	Event (preferred term)	Date of Onset	Study day of onset	Relationship to study drug	Outcome
Telbivudine							
003-205	AUV-118	Mild viral fever on the day of liver biopsy	Pyrexia	07-Mar-2005	370	No	Resolved; no residual effects
003-235	AUV-25	Left loin pain	Back pain	15-Mar-2004	NA	No	Resolved; no residual effects
008-027	AUV-6	Renal stone	Nephrolithiasis	05-Sep-2003	22	No	Resolved; no residual effects
	AUV-9	Recent retina detachment, partial	Retinal detachment	08-Dec-2003	116	No	Resolved; no residual effects
008-042	AUV-31	Nasopharyngeal carcinoma	Nasopharyngeal cancer	22-Mar-2004	160	No	Continuing
008-046	AUV-160	Fever	Pyrexia	13-Jun-2005	617	No	Resolved; no residual effects
008-078	AUV-207	Urethra stone	Calculus urinary	31-Oct-2005	613	No	Resolved; no residual effects
008-088	AUV-92	Acute cholecystitis	Cholecystitis acute	05-Jan-2005	297	No	Resolved; no residual effects
012-001	AUV-28	Possible drug-induced myopathy	Myopathy	09-Feb-2004	300	Yes	Resolved; no residual effects

Site-patient ID	Event ID	Event (verbatim)	Event (preferred term)	Date of Onset	Study day of onset	Relationship to study drug	Outcome
012-006	AUV-32	Post liver biopsy hypotension	Hypotension	13-May-2004	367	No	Resolved; no residual effects
012-020	AUV-3	Gallbladder perforation	Gallbladder perforation	28-Aug-2003	NA	No	Resolved; no residual effects
012-022	AUV-119	Pneumonia	Pneumonia	20-Feb-2005	500	No	Resolved; no residual effects
016-012	AUV-156	Liver failure	Hepatic failure	29-Jul-2005	533	Yes	Resolved; no residual effects
019-003	AUV-152	Vestibular neuronitis	Vestibular neuronitis	30-May-2005	708	No	Resolved; no residual effects
	AUV-171	Anxiety neurosis	Anxiety disorder	11-Jun-2005	720	No	Resolved; no residual effects
019-010	AUV-107	Dengue fever	Dengue fever	07-Jan-2005	424	No	Resolved; no residual effects
019-017	AUV-122	Viral fever	Pyrexia	17-Mar-2005	372	No	Resolved; no residual effects
035-023	AUV-138	Hepatocellular carcinoma	Hepatic neoplasm malignant	11-May-2005	433	No	Resolved; no residual effects
036-003	AUV-183	Anal fistula	Anal fistula	11-Aug-2005	708	No	Resolved; no residual effects
046-026	AUV-41	Motion sickness	Motion sickness	18-Jul-2004	332	No	Resolved; no residual effects
046-042	AUV-101	Upper respiratory tract infection	Upper respiratory tract infection	06-Jan-2005	385	No	Resolved; no residual effects
057-001	AUV-56	Malignant right breast lump	Breast cancer	14-Sep-2004	415	No	Resolved; no residual effects
057-016	AUV-58	Pericarditis	Pericarditis	24-Sep-2004	408	No	Resolved; no residual effects
057-030	AUV-54	Pneumonia	Pneumonia	16-Sep-2004	366	No	Resolved; no residual effects
057-064	AUV-20	Neck abscess	Abscess neck	03-Nov-2003	NA	No	Resolved; no residual effects
057-087	AUV-35	Fractured left ankle	Ankle fracture	10-Jun-2004	135	No	Resolved; no residual effects

	AUV-69	Cellulitis left shin and ankle	Cellulitis	29-Oct-2004	276	No	Resolved; no residual effects
057-089	AUV-23	Vasovagal episode after liver biopsy	Syncope vasovagal	02-Feb-2004	NA	No	Resolved; no residual effects
057-131	AUV-176	Laceration left foot	Skin laceration	17-Jul-2005	467	No	Resolved; no residual effects
061-008	AUV-89	Hepatic lesion	Hepatic lesion	22-Dec-2004	469	No	Resolved; no residual effects
	AUV-132	Drug induced hypoglycemia	Hypoglycaemia	09-Mar-2005	546	No	Resolved; no residual effects
	AUV-126	Hamartoma	Hamartoma	30-Mar-2005	567	No	Continuing
061-035	AUV-44	Musculoskeletal chest pain	Musculoskeletal chest pain	20-Aug-2004	275	No	Resolved; no residual effects
068-004	AUV-73	Oesophageal variceal bleeding	Oesophageal varices haemorrhage	11-Nov-2004	409	No	Resolved; no residual effects
	AUV-87	Bleeding from gastric fundus varice	Gastric varices haemorrhage	10-Dec-2004	438	No	Resolved; no residual effects
	AUV-227	Hepatic encephalopathy Attack	Hepatic encephalopathy	17-Sep-2005	719	No	Resolved; no residual effects
068-021	AUV-78	Hyper Creatinine Kinase measurement at scheduled visit	Blood creatine phosphokinase increased	25-Nov-2004	276	No	Resolved; no residual effects
071-001	AUV-14	Coronary artery disease	Coronary artery disease	23-Dec-2003	100	No	Continuing
	AUV-134	Congestive heart failure	Cardiac failure congestive	30-Mar-2005	563	No	Continuing
	AUV-263	Dyspnoe	Dyspnoea	20-Apr-2005	584	No	Resolved; no residual effects
071-043	AUV-121	Creatine kinase elevation	Blood creatine phosphokinase increased	16-Mar-2005	366	Yes	Resolved; no residual effects
087-013	AUV-267	Renal colic nephrolithiasis	Nephrolithiasis	27-Feb-2006	719	No	Resolved; no residual effects
089-002	AUV-177	Atherosclerotic coronary artery disease	Coronary artery disease	08-Jun-2005	447	No	Resolved; no residual effects
118-008	AUV-246	Acute exacerbation of	Hepatitis B	06-Jan-2006	705	No	Resolved; no residual

		hepatitis					effects
122-037	AUV-37	Spermophlebectasia	Spermatic cord disorder	14-Jun-2004	103	No	Resolved; no residual effects
127-044	AUV-75	Postural hypotension	Orthostatic hypotension	30-Aug-2004	176	No	Continuing
		Pituitary adenoma	Pituitary tumour benign	03-Nov-2004	241	No	Continuing
	AUV-185	Atrial fibrillation	Atrial fibrillation	14-Jul-2005	494	No	Resolved; no residual effects

Source: Table 12-10 Study Report NV-02B-007

Medical Officer Comments: *Narratives for each of the SAEs reported in patients treated with telbivudine were reviewed. The Medical Officer is in agreement with the applicant's assessment of relationship to study medication with one exception. Patient number 068-021, a 22 year-old Caucasian male, developed CK elevations starting at week 24 (CK 689 U/L), and then again at week 32 (CK 303 U/L). The maximum CK level reported in this patient was 1645 U/L; and his baseline CK was 89 U/L. At week 40, generalized muscle weakness and fatigue were reported and a CK level of 1645 U/L was noted, a value approximately 9 x ULN (ULN, 179 U/L). The study medication was stopped at that time, and CK values decreased (CK 203 U/L one month after stopping); when telbivudine was restarted the patient continued to have intermittent CK elevations (CK 584 U/L noted approximately 2 months after restarting telbivudine). An EMG study of bilateral upper and lower extremities was reportedly normal. This patient was a competitive arm wrestler, and the applicant considered these events unrelated to telbivudine; however, given the known safety profile of this drug, and the positive de-challenge and re-challenge, the CK elevations, and generalized weakness and fatigue were probably related to telbivudine.*

The SAEs experienced by patients treated with lamivudine were also reviewed, and the Medical Officer agrees with the applicant's assessment of relatedness to study medication in all but one case. Patient 126-010 experienced a hepatitis flare while on lamivudine, which was subsequently discontinued. This event was considered related to lamivudine. However, investigators attributed exacerbations of hepatitis to study medication inconsistently, as a number of other SAEs of hepatitis flares, acute exacerbations of hepatitis B, or other hepatic SAEs (e.g. ALT elevation, hepatic encephalopathy, liver failure associated with increased HBV DNA) were considered unrelated to study medication, and rather, related to underlying disease process. Review of the narratives revealed a total of 12 patients with hepatitis flares or acute hepatitis B exacerbations (on-treatment) considered serious adverse events in the study, 9 on lamivudine (8 considered unrelated; 1 related) and 3 on telbivudine (2 considered unrelated; 1 related), not including hepatocellular carcinoma reported as an SAE in 2 lamivudine recipients and 1 telbivudine recipient. The applicant noted that 10 lamivudine recipients and 4 telbivudine recipients experienced SAEs of hepatitis B exacerbation, including hepatitis exacerbation, ALT flare, hepatic failure, hepatic encephalopathy or hepatocellular carcinoma.

Additionally, SAEs associated with liver biopsy (e.g. fever, hypotension, abdominal pain, perforated gallbladder, vasovagal syncope) were reported in 11 patients in this study regardless of treatment group.

Table 38. Serious Adverse Events (on-Treatment) which occurred in at least 2 patients are shown in the following table.

Serious Adverse Event PT	Lamivudine N=687	Telbivudine N=680
Coronary artery Disease	0	2
Pyrexia or fever	0	3
Pneumonia	0	2
CK increased	0	2
Nephrolithiasis or urinary calculus	0	3
Hypotension or orthostatic hypotension	0	2
ALT increased	2	0
Appendicitis	2	0
Hepatic neoplasm, malignant	2	1
Hepatitis B	2	1
Hepatitis E	2	0
Post-procedural pain	2	0
Renal colic	2	0
Wound infection	2	0

Source: A_AE dataset for Study 007

Medical Officer Comments: *As shown in the table above, there was a different pattern of serious adverse events in the two treatment groups. Notably, in the telbivudine group 3 patients experienced fever and 3 experienced kidney stones in comparison to none in the lamivudine group. The imbalance between treatment groups with regard to nephrolithiasis was not noted previously in the review of the 52 week safety data. However, renal colic was considered an SAE in 2 patients receiving lamivudine, and renal colic is generally due to nephrolithiasis. Thus, the difference noted here may be due simply to differences in coding adverse events.*

As shown in the table below, a total of 5 patients in NV-2B-007 had SAE's (2 lamivudine, 3 telbivudine-treated patients) which the investigator considered possibly related to study drug, as shown in the following table.

Table 39. Serious Adverse Events Considered Drug-Related

Table 12-9 Serious adverse events attributed to study drug

Study drug	Site-patient ID	Grade & SAE	Intervention required	Event resolved	Action taken with study drug
Lamivudine	008-079	Grade 2 urticarial rash	Yes	Yes	Discontinued
	126-010	Grade 2 hepatitis flare	Yes	Yes	Discontinued
Telbivudine	012-001	Grade 2 myopathy	No	Yes	Interrupted
	016-012	Grade 4 liver failure	Yes	Yes	Discontinued
	071-043	Grade 4 elevated CK	No	Yes	None

Source: Table 14.3.2.2

Medical Officer Comments: *See comments above regarding an additional SAE considered at least possibly drug-related by this reviewer in patient 068-021 who experienced CK elevations while on telbivudine.*

Off-Treatment SAEs

The applicant reported only one off-treatment SAE in a lamivudine patient who had discontinued study medication due to efficacy at one year. Study drug was restarted approximately 8 months later due to increasing HBV DNA and ALT levels. This 62 year-old Chinese male had a history of ischemic heart disease, acute myocardial infarction, hypertension, hyperlipidemia and unstable angina, developed sinus bradycardia, and possible acute MI on ECG and was hospitalized the same day that lamivudine was re-started. CK, CK-MB and troponin T levels were within normal limits, and the patient did not experience pain during a stress-ECG study; however, 2-3 mm ST segment depressions were noted in the inferolateral leads. An angiogram was refused and the patient was diagnosed with "atypical chest pain". This event was not considered related to study medication.

Medical Officer Comments: *The medical officer agrees with the applicant's assessment that this event was probably not related to study medication, but rather to underlying cardiac disease.*

Post-Treatment SAEs

One post-treatment SAE was reported in a patient who received lamivudine. In patient 054-021, a 21 year-old Korean male, lamivudine was discontinued due to increased HBV DNA and ALT levels after week 60 laboratory values were obtained. Approximately 3 weeks after study discontinuation, the patient was involved in a traffic accident and was hospitalized. This event was not considered related to study medication.

Medical Officer Comments: *The medical officer agrees that this SAE was not likely related to study medication.*

Dropouts/Discontinuations due to Adverse Events

From baseline to the end of study, 26/687 (3.8%) lamivudine recipients and 27/680 (4%) telbivudine recipients interrupted or discontinued study medication due to an adverse event; while in the first year of the study, 18/687 (2.6%) lamivudine- an 19/687 (2.8%) telbivudine-treated patients discontinued or interrupted therapy because of an adverse event. The most

common adverse event resulting in treatment discontinuation/ was increased CK interruption in the telbivudine group and increased ALT in the lamivudine group. Adverse events more common in the telbivudine than lamivudine group which occurred in at least 2 patients were diarrhea, nausea, fatigue, increased CK, myalgia, and myopathy.

Table 40. Adverse Events resulting in Drug Discontinuation or Dose Interruption from Baseline to End-of-Study in Safety Population

Adverse Event SOC and PT	Lamivudine N= 687	Telbivudine N=680
Patients reporting AE	26 (3.8)	27 (4.0)
Cardiac Disorders:	0	1
Cardiac failure, congestive	0	1
Gastrointestinal disorders:	4 (0.6)	10 (1.5)
Diarrhea	1 (0.1)	**4 (0.6)**
Nausea	0	**4 (0.6)**
Abdominal pain	1	1
Vomiting	2 (0.3)	0
Abdominal distension	0	1
Abdominal tenderness	0	1
Dyspepsia	1	0
Gastric varices, hemorrhage	0	1
Gastritis	0	1
Loose stools	0	1
General disorders and site administration:	3 (0.4)	3 (0.4)
Fatigue	0	**2 (0.3)**
Asthenia	0	1
Malaise	1	0
Mucous membrane disorder	1	0
Pyrexia	1	0
Hepatobiliary disorders:	1	1
Hepatic failure	0	1
Hepatic pain	1	0
Immune system disorders	1	0
Infections and Infestations:	10 (1.5)	4 (0.6)
Hepatitis B	6 (0.9)	2 (0.3)
Investigations:	2 (0.3)	8 (1.2)
Blood CK increased	1	**6 (0.9)**
ALT increased	1	1
Blood CK MB increased	0	1
Blood potassium decreased	0	1
Metabolism and nutrition	1	0

disorders		
Musculoskeletal and connective tissue disorders	0	5 (0.7)
Myalgia	0	2
Myopathy	0	2
Pain in extremity	0	1
Neoplasms, benign, malignant, and unspecified	3 (0.4)	1 (0.1)
Nervous system disorders	3 (0.4)	2 (0.3)
Reproductive system and breast disorders	0	1
Respiratory, thoracic, and mediastinal disorders	0	1
Skin and subcutaneous tissue disorders	1	0

A total of nine patients (7 lamivudine; 2 telbivudine) discontinued study medication due to SAEs. SAEs resulting in treatment discontinuation included hepatitis exacerbation/flare (3), hepatic encephalopathy (1), Grade 3 ALT elevation (1), urticarial rash (1), and multiple myeloma (1) in the lamivudine group; and liver failure (1), and congestive heart failure (1) in the telbivudine group. SAEs resulting in treatment interruption (8 total) included hepatocellular carcinoma (2), dizziness and malaise (1), appendicitis (1) in the lamivudine group; and myopathy (1), gastric variceal hemorrhage (1), Grade 1 CK increase (1), and pituitary adenoma (1) in the telbivudine group.

Significant Adverse Events

Adverse events and laboratory abnormalities identified as significant adverse events in this study included CK elevation, myopathy, and ALT flares.

CK Elevation
Creatine kinase (CK) elevation was reported as an adverse event in 84/680 (12.4%) telbivudine patients and 52/687 (7.6%) lamivudine-treated patients over the two year study period. In the telbivudine group, the adverse event, blood creatine phosphokinase elevation was reported as Grade 1 in 41 patients, Grade 2 in 25 patients, Grade 3 in 13 patients, and Grade 4 in 14 patients (patients having more than one AE of CK elevation were counted more than once) .Among lamivudine-treated patients, 37 patients experienced a Grade 1 CK elevation, 11 had Grade 2 CK increase, 1 had a Grade 3 CK increase, and 9 had Grade 4 increase in CK. A total of 6 telbivudine and 1 lamivudine patient interrupted or discontinued study medication due to an adverse event of CK elevation.

Medical Officer Comments: *Although Grade 1 CK elevations were reported as adverse events in similar numbers of lamivudine- and telbivudine-treated patients, more patients in the telbivudine group experienced Grades 2-4 CK elevations reported as adverse events.*

New onset CK elevation of Grade 1 through 4 severity in this study is summarized in the following table. Among telbivudine-treated patients, 537/680 (79%) experienced any CK elevation in comparison to 338/687 (49.2%) lamivudine treated patients. The majority of CK elevations were Grade 1-2. Note that if a patient had both Grade 1/2 and Grade 3/4 CK elevation, that patient was counted only as having a Grade 3/4 CK elevation.

Table 41. New Onset CK Elevations (Baseline to Week 104)

Table 12-26 **Summary of new-onset Grade 1/2 and Grade 3/4 CK elevations, Baseline to End of Study – overall Safety population**

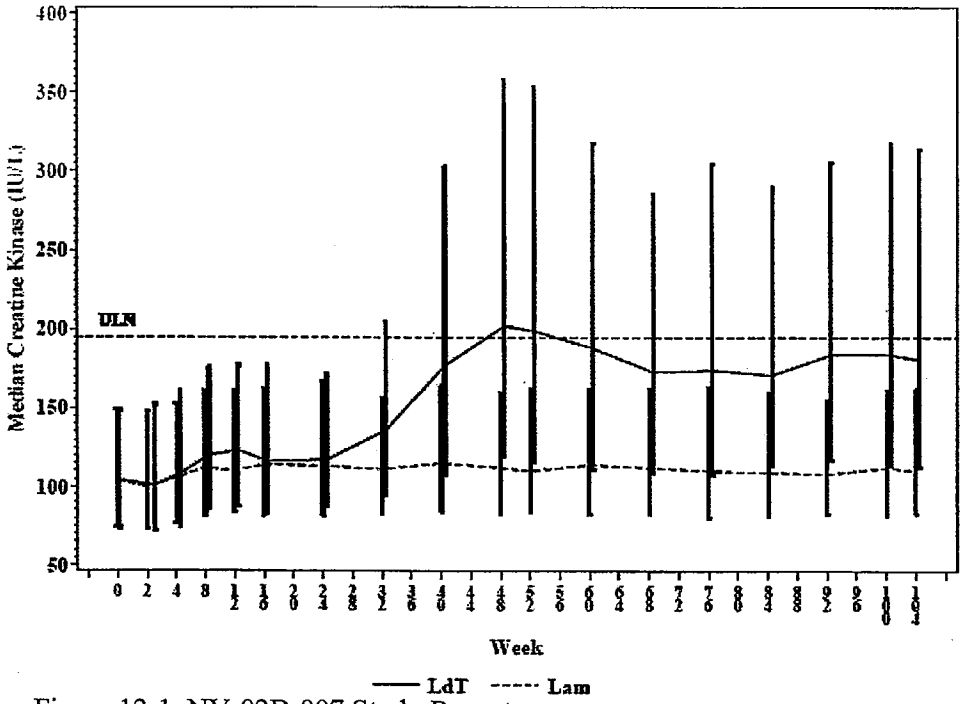
	Grade 1/2				Grade 3/4			
	Lamivudine		Telbivudine		Lamivudine		Telbivudine	
New-onset CK elevation	(N=687) n (%)		(N=680) n (%)		(N=687) n (%)		(N=680) n (%)	
Baseline to End of Study	310	(45.1)	449	(66.0)	28	(4.1)	88	(12.9)
Post Week 52	196	(28.5)	405	(59.6)	9	(1.3)	56	(8.2)

Source: Table 12-26 NV-02B-007 study Report

The applicant showed that the median CK values in the first 24 weeks of treatment were similar to median baseline levels in both treatment groups. However, after week 24, median CK valued increased in telbivudine recipients, peaking around week 52 and remaining relatively constant thereafter; while in lamivudine recipients the median CK values remained relatively constant from baseline to week 104 (see Figure 8 below).

Figure 8. Median CK values (Baseline to Week 104)

Figure 12-1 Median CK values (and interquartile ranges) by study visit, Baseline to Week 104 – overall Safety population



Source: Figure 12-1. NV-02B-007 Study Report

The incidence of new-onset Grade 3 or 4 CK elevation was highest between weeks 24 and 52 in telbivudine recipients. Most patients with Grade 3 or 4 CK elevations had resolution to Grade < 3 by the next scheduled or unscheduled visit in both treatment groups; however, a higher proportion of lamivudine than telbivudine recipients had resolution to normal or baseline CK value. While the majority of patients with new-onset CK elevation in both treatment groups had a single Grade 3 or 4 elevation (86% lamivudine, 60% telbivudine), more telbivudine patients had more than one episode of Grade 3 or 4 CK elevation (28/88, 32%) than lamivudine patients (4/28, 14%).

Note that for this study, the applicant used a Toxicity Table modified from the 1992 Division of Aids (DAIDS) Table for Grading Severity of Adult Experiences. For some of the safety laboratory assessments, including CK, toxicity grading differs significantly between the table used for toxicity grading in this study and the DAIDS toxicity table published in 2004, as shown in the following table.

Table 42. Comparison of Toxicity Grading for CK Elevations used for Study 007 (1992 DAIDS Table) and in more recent Toxicity Table (2004 DAIDS Table)

Toxicity Grade	Modified 1992 DAIDS Table used for Study 007	2004 DAIDS Toxicity Table
Grade 1	1-3 x ULN	3-5.9 x ULN
Grade 2	> 3 - 7 x ULN	6-9.9 x ULN
Grade 3	>7 – 10 x ULN	10-19.9 x ULN
Grade 4	> 10 x ULN	≥ 20 x ULN

ULN = upper limit of normal for laboratory value

***Medical Officer's Comments**: Because of the differences in toxicity tables, CK toxicity grading in this study is more conservative than if the 2004 DAIDS toxicity table had been used.*

Myopathy

The overall incidence of adverse events in the musculoskeletal and connective tissue disorder MedDRA system organ class (SOC) were similar in the two treatment groups (115/687, 16.7% for lamivudine and 119/680, 17.5% for telbivudine). However, 4 cases of myopathy or myositis were reported in the telbivudine group compared to 1 in the lamivudine group. These cases are summarized in the following table.

Table 43. Patients with Myopathy and Myositis in Study 007

Table 12-12 Occurrence of myopathy and myositis – Overall safety population

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

Source: Table 12-12, NV-02B-007 Study Report

***Medical Officer Comments**: Only one of these events was considered serious, myopathy in patient 012-001. In each case of myopathy, telbivudine was either 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 event to study medication for patients 007-012-001 and 054-031 (drug-related events in both cases). This reviewer disagrees with the assessment made for patient 057-123 in that the event could be considered at least possibly related as there was a*

temporal relationship, accompanying CK elevations, and positive de-challenge in that patient. For the other two patients, 008-026 and 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 008-026, the event resolved quickly while the patient remained on treatment (lamivudine); and in patient 008-019, the event was described as right arm pain (and coded as myositis), which also resolved on treatment.

Association of Muscle-related Adverse Events with CK Elevation

The applicant analyzed on-treatment adverse events potentially associated with myopathic or muscle injury. These included asthenia, fatigue, malaise, muscular weakness, musculoskeletal discomfort, musculoskeletal pain, myalgia, myopathy, myositis, pain in extremity and polymyositis. The following table shows the applicant's analysis of the occurrence of Grade 3 or 4 CK elevation during one or more of these adverse events (i.e. between onset and resolution of AE). Note that for both treatment groups, the majority of Grade 3 or 4 CK elevations were not temporally associated with a muscle-related adverse event. However, a higher proportion of Grade 3 or 4 CK elevations in the telbivudine-treated patients occurred during a muscle-related adverse event or within 30 days of a muscle-related adverse event in comparison to lamivudine-treated patients.

Table 44. New Onset Grade 3 or 4 CK Elevation and Association with Musculoskeletal Adverse Events

Table 12-31 Summary of occurrence of new-onset Grade 3/4 CK and AEs possibly related to myopathic/muscle injury process – overall Safety population

	Lamivudine (N=687) n (%)	Telbivudine (N=680) n (%)
Number of episodes of Grade 3/4 CK	32	130
Occurred within an AE[1,2]	1 (3.1)	19 (14.6)
Occurred outside an AE[2,3]	10 (31.3)	15 (11.5)
Occurred within an AE +/- 30 Days	2 (6.3)	22 (16.9)
Occurred outside an AE +/- 30 Days	9 (28.1)	12 (9.2)
No selected musculoskeletal AEs reported	21 (65.6)	96 (73.8)

[1] Grade 3/4 CK occurred within an AE is defined as a Grade 3/4 CK occurring between onset date and resolution date of an AE.
[2] AE terms possibly related to myopathic/muscle injury process are asthenia, fatigue, malaise, muscular weakness, musculoskeletal discomfort, musculoskeletal pain, myalgia, myopathy, myositis, pain, pain in extremity, and polymyositis.
[3] Grade 3/4 CK occurred outside an AE is defined as a Grade 3/4 CK occurring before onset date of an adverse event or after resolution date of an AE.

Source: Study Report Table 12-31

***Medical Officer Comments**: A similar analysis was done to determine the proportion of patients who experienced a muscle-related adverse event within 30 days of the CK elevation. Adverse events were reported within 30 days of new-onset Grade 1 through Grade 4 CK elevation in 19/338 (5.6%) lamivudine recipients and in 51/537 (9.5%) telbivudine recipients.*

Discontinuations due to Musculoskeletal Adverse Events or CK Elevation

A total of 2 lamivudine-treated patients and 11 telbivudine-treated patients discontinued or interrupted study medication due to musculoskeletal adverse events or CK elevation. The

adverse events malaise, asthenia, and fatigue were also included as potential muscle-related adverse events. Adverse events resulting in treatment interruption or discontinuation are described for each of these patients in the following table.

Table 45. Discontinuations and Interruptions to CK and Musculoskeletal Adverse Events

Table 12-13 Patients who discontinued or interrupted study drug due to elevated creatine kinase, musculoskeletal events, or other selected adverse events, Baseline to End of Study – overall Safety population

Site-patient ID	Event & grade	SAE	Attribution to study drug	Date of onset	Study day of onset	Date of resolution	Study drug action
Lamivudine							
079-004	CK Grade 4	No	Reasonably or possibly	13-May-2005	477	19-May-2005	Discontinued
092-016	Malaise Grade 3	Yes	Not reasonably or possibly related	28-Apr-2004	28	03-May-2004	Interrupted
Telbivudine							
012-001	CK Grade 2	No	Reasonably or possibly related	20-Jan-2004	280	14-Apr-2004	Interrupted*
	Myopathy Grade 2	Yes	Reasonably or possibly related	09-Feb-2004	300	16-Mar-2005	Interrupted
025-008	CK Grade 2	No	Reasonably or possibly related	22-Jul-2004	274	26-Oct-2004	Discontinued
054-031	Myopathy Grade 2	No	Reasonably or possibly related	Jan-2005	328	Aug-2006	Discontinued
068-021	CK Grade 1	Yes	Not reasonably or possibly related	30-Sep-2004	220	02-Dec-2004	Interrupted
071-043	Myalgia Grade 1	No	Reasonably or possibly related	17-Mar-2005	367	30-Mar-2005	Interrupted
105-012	Fatigue Grade 2	No	Reasonably or possibly related	01-Oct-2004	260	28-Sep-2005	Interrupted
	Myalgia Grade 2	No	Not reasonably or possibly related	Aug-2004	199	28-Oct-2005	Interrupted
119-004	CK Grade 4	No	Not reasonably or possibly related	25-Jan-2006	702	07-Feb-2006	Interrupted
119-005	Pain in extremity Grade 1	No	Reasonably or possibly related	28-Mar-2005	410	01-Jul-2005	Interrupted
122-054	Fatigue Grade 1	No	Reasonably or possibly related	03-Mar-2005	332	28-Jun-2005	Discontinued
125-003	CK Grade 1	No	Reasonably or possibly related	03-Sep-2004	172	12-Jul-2005	Interrupted
	CK-MB Grade 1	No	Reasonably or possibly related	05-Mar-2005	355	15-Jul-2005	Interrupted
	CK Grade 4	No	Reasonably or possibly related	26-Dec-2005	651	22-Mar-2006	Interrupted
132-002	CK Grade 2	No	Reasonably or possibly related	14-Sep-2005	546	16-Feb-2006	Interrupted
	Asthenia Grade 1	No	Reasonably or possibly related	20-Mar-2005	368	26-Dec-2005	Interrupted

Medical Officer Comments: *The narrative summaries for the telbivudine-treated patients were reviewed, and this reviewer concluded that all of these adverse events were at least possibly related to telbivudine.*

Neuropathic Adverse Events

Because peripheral neuropathy has recently been identified as a potential safety concern with telbivudine, neuropathic adverse events in Study 007 were reviewed. Overall, 19/687 (2.8%) lamivudine patients and 24/680 (3.5%) telbivudine patients experienced on-treatment adverse events in the Nervous systems disorders SOC from baseline to end-of-study (week 104). A summary of nervous system adverse events in this study is shown in the following table.

Table 46. Summary of Treatment-emergent Neuropathic Adverse Events in Study 007

Table 12-14 Summary of on-treatment neuropathic or other sensory AEs – Safety overall population

	Lamivudine (N=687)		Telbivudine (N=680)	
Body System/Preferred Term	n	(%)	n	(%)
Patients reporting a nervous system AE	19	(2.8)	24	(3.5)
Hypoaesthesia	7	(1.0)	7	(1.0)
Dysgeusia	2	(0.3)	8	(1.2)
Paraesthesia	6	(0.9)	4	(0.6)
Paraesthesia oral	0		2	(0.3)
Polyneuropathy	0		2	(0.3)
Anosmia	0		1	(0.1)
Dysaesthesia	1	(0.1)	0	
Facial palsy	1	(0.1)	0	
Intercostal neuralgia	0		1	(0.1)
Neuralgia	1	(0.1)	0	
Neuropathic pain	0		1	(0.1)
Sciatica	0		1	(0.1)
Sensory loss	0		1	(0.1)
Tremor	1	(0.1)	0	

Source: Table 12-14, Study Report NV-02B-007

Note that in this study 2 telbivudine-treated patients experienced "polyneuropathy." Neither AE was considered serious. The applicant provided a brief case report for each, reviewed here. The first patient, a 48 year-old Chinese male developed polyneuropathy (Grade 1) approximately 1 year after starting telbivudine. Telbivudine was continued and this adverse event continued through the week 104 study visit, and the patient subsequently enrolled in the follow-on study, 022. He was continued on telbivudine for an additional 104 weeks in that study, and at week 52 experienced "leg numbness". Treatment for this adverse event included imipramine and prosultiamine (vitamin B12). No further information was available. The second patient was a 62 year-old Caucasian female who developed left leg weakness and paraesthesia reported as polyneuropathy (grade 2) occurring approximately 2 months after stopping telbivudine. An initial EMG was reportedly abnormal, and follow-up EMG suggested improvement of "multiple mononeuritis-axonal sensitive neuropathy" affecting the left sural and peroneal nerves. This latter adverse event was considered related to study drug by the investigator.

Additionally, one case of peripheral sensory neuropathy was reported in the post-treatment period. However, this patient reportedly had a 10 year history of progressive peripheral and autonomic neuropathy, which potential confounds interpretation in this case.

Medical Officer Comments: *Other adverse events not coded as peripheral neuropathy but considered symptoms of peripheral neuropathy included hypoaesthesia (7 patients), neuralgia (1 patient), neuropathic pain (1patient), paraesthesia (4 patients), sensory loss (1patient) in the telbivudine group, and dysaesthesia (1patient), hypoaesthesia (7 patients), paraesthesia (6 patients) in the lamivudine group. There was also an imbalance between treatment groups for the adverse event, dysgeusia, abnormal taste, with 8 patients in the telbivudine group, and 2 in the lamivudine reporting this AE.*

ALT Flares

On-treatment ALT flares (hepatitis flares) using the AASLD definition (ALT > 2 x baseline and > 10 x ULN) were reported less commonly in telbivudine, 28/680 (4.1%) than in lamivudine 51/687, (7.4%). Most patients experienced on-treatment ALT flares in the first 24 weeks of the study in both treatment groups. The following table shows the applicant's analysis of on-treatment ALT flares by 6-month time intervals. Patients who experienced an ALT flare during more than 1 time period were counted for each time period in this analysis.

Table 47. ALT Flares

Table 12-21 Summary of the on-treatment ALT flare phenomenon by 6-month intervals using the AASLD definition of ALT flare – overall Safety population

	Lamivudine		Telbivudine	
Analysis period	**n/N**	**(%)**	**n/N**	**(%)**
Baseline to Week 24	21/687	(3.1)	19/680	(2.8)
Week 24 to Week 52	11/673	(1.6)	2/669	(0.3)
Week 52 to Week 76	10/647	(1.5)	4/649	(0.6)
Week 76 to Week 104	12/605	(2.0)	6/616	(1.0)
Week 24 to End of Study	32/673	(4.8)	10/669	(1.5)
	n/N	(%)	n/N	(%)
Total, overall	51/687	(7.4)	28/680	(4.1)
Total, HBeAg-positive patients	45/455	(9.9)	24/445	(5.4)
Total, HBeAg-negative patients	6/232	(2.6)	4/235	(1.7)

Medical Officer Comments: *For each of the time intervals, proportionately more lamivudine than telbivudine-treated patients experienced ALT flares on-treatment. Additionally, although there were fewer HBeAg-negative patients in the study, the proportion of HBeAg-negative patients who experienced an on-treatment ALT flare was lower than the proportion of HBeAg-positive patients in each treatment group.*

Off-Treatment ALT Flares

In this study, 39 telbivudine- and 21 lamivudine-treated patients discontinued treatment because criteria for discontinuation due to efficacy were met and were evaluated in the "off-treatment" period. Among these patients, 1 telbivudine-treated patient experienced an ALT flare off-treatment based on the AASLD definition.

Post-Treatment ALT Flares

Patients who discontinued treatment prior to week 104, and patients who at week 104 elected not to enroll in the follow-on study 022, entered the 4 month post-treatment monitoring period. Only a small proportion of the study population (20% lamivudine recipients and 15% telbivudine recipients) were evaluated post-treatment in this study. Based on the AASLD definition, 7/ 134 (5.2%) lamivudine- and 8/96 (8.3%) telbivudine-treated patients monitored for 4 months post-treatment experienced an ALT flare.

Common Adverse Events

In this study, 529/687 (77%) lamivudine- and 551/680 (81%) telbivudine-treated patients experienced at least one treatment-emergent adverse event form baseline to the end of the study. This represents an increase from the Week 52 data, in which 70% lamivudine recipients and 75% telbivudine recipients experienced at least one treatment-emergent adverse event from baseline to the Week 52 visit. The most frequent adverse events in both treatment groups were upper respiratory tract infection and nasopharyngitis, as shown in the following table. The common adverse events (> 3%) more frequent in the telbivudine than the lamivudine group included upper respiratory tract infection, nasopharyngitis, fatigue, increased blood creatine phosphokinase (CK), post-procedural pain, cough, diarrhea, nausea, rash, back pain, pyrexia, and myalgia.

Table 48. Treatment-Emergent Common (> 2%) Adverse Events

Table 12-4 On-treatment adverse events by decreasing frequency for events occurring between Baseline and End of Study in more than 2% of patients on telbivudine – overall Safety population

	Lamivudine (N=687)		Telbivudine (N=680)	
Preferred term	n	(%)	n	(%)
Patients reporting an adverse event	529	(77.0)	551	(81.0)
Upper respiratory tract infection	111	(16.2)	119	(17.5)
Nasopharyngitis	90	(13.1)	102	(15.0)
Fatigue	83	(12.1)	91	(13.4)
Blood creatine phosphokinase increased	51	(7.4)	84	(12.4)
Headache	92	(13.4)	79	(11.6)
Post procedural pain	45	(6.6)	49	(7.2)
Cough	41	(6.0)	46	(6.8)
Influenza	56	(8.2)	46	(6.8)
Diarrhoea	39	(5.7)	44	(6.5)
Abdominal pain upper	47	(6.8)	43	(6.3)
Nausea	37	(5.4)	42	(6.2)
Pharyngolaryngeal pain	29	(4.2)	35	(5.1)
Arthralgia	35	(5.1)	34	(5.0)
Rash	21	(3.1)	33	(4.9)
Dizziness	40	(5.8)	32	(4.7)
Back pain	30	(4.4)	31	(4.6)
Pyrexia	23	(3.3)	31	(4.6)
Abdominal pain	28	(4.1)	27	(4.0)
Myalgia	15	(2.2)	25	(3.7)
Dyspepsia	37	(5.4)	24	(3.5)
Alanine aminotransferase increased	30	(4.4)	23	(3.4)
Insomnia	21	(3.1)	21	(3.1)
Asthenia	11	(1.6)	18	(2.6)
Hypertension	14	(2.0)	18	(2.6)
Pruritus	20	(2.9)	16	(2.4)
Preferred term	**n**	**(%)**	**n**	**(%)**
Vomiting	16	(2.3)	16	(2.4)
Gastritis	8	(1.2)	16	(2.4)
Urinary tract infection	8	(1.2)	16	(2.4)
Abdominal distension	13	(1.9)	15	(2.2)
Influenza like illness	17	(2.5)	15	(2.2)
Anorexia	7	(1.0)	14	(2.1)
Constipation	12	(1.7)	14	(2.1)
Toothache	15	(2.2)	14	(2.1)

Source: Table 12-4 007 Study Report

Adverse Events Considered Drug-Related

The most common (> 2%) adverse events reported from baseline to end-of-study (to week 104) which were considered at least possibly or reasonably related by the clinical investigator are

shown in the following table. The proportion of patients in the telbivudine group with on-treatment drug-related adverse events was somewhat higher in the telbivudine than the lamivudine group. common drug-related adverse events more frequent in the telbivudine than the lamivudine treatment arm included increased CK, nausea, and fatigue.

Table 49. Drug-Related Adverse Events in Study 007

Table 12-5 Study-drug-attributed adverse events occurring between Baseline and End of Study in more than 2% of telbivudine recipients – overall Safety population

SOC/preferred term	Lamivudine (N=687) n (%)	Telbivudine (N=680) n (%)
All patients with a drug-attributed AE	159 (23.1)	197 (29.0)
Investigations (laboratory abnormalities)	56 (8.2)	77 (11.3)
CK increase	28 (4.1)	53 (7.8)
ALT increase	17 (2.5)	15 (2.2)
Gastrointestinal disorders	57 (8.3)	63 (9.3)
Nausea	17 (2.5)	22 (3.2)
General disorders and administration site conditions	32 (4.7)	56 (8.2)
Fatigue	20 (2.9)	34 (5.0)
Nervous system disorders	35 (5.1)	45 (6.6)
Headache	25 (3.6)	23 (3.4)
Skin and subcutaneous tissue disorders	17 (2.5)	27 (4.0)
Infections and infestations	21 (3.1)	24 (3.5)
Musculoskeletal and connective tissue disorders	18 (2.6)	16 (2.4)

Source: Table 13.3.1.3.2.3 in 007 Study Report

Medical Officer Comments: *Attribution of an adverse event to study medication by the investigator is highly subjective, and other safety data must be taken into account when drawing conclusions regarding the relationship between study drug and an adverse event.*

Moderate to Severe Adverse Events

Moderate to Severe (Grades 2-4) adverse events were reported in 187/687 (27.2%) lamivudine- and 203/680 (29.9%) telbivudine-treated patients through the end of the study. The most common (> 2%) moderate-severe adverse events are shown in the following table. Those events more frequent in the telbivudine group included increased CK, upper respiratory infection, and fever,; whereas increased ALT, AST, lipase, back pain, and headache were more common in the lamivudine group.

Table 50. Moderate to Severe On-Treatment Adverse Events in ≥1% Telbivudine Recipients (Baseline to End-of-Study)

Adverse Events Preferred Term	Lamivudine N=687	Telbivudine N=680
Fatigue	9 (1.2)	**9 (1.3)**
Pyrexia	2 (0.3)	**9 (1.3)**
Upper Respiratory Infection	11 (1.6)	**19 (2.8)**
Nasopharyngitis	9 (1.3)	9 (1.3)
Blood CK increased	21 (3.1)	**51 (7.5)**
ALT increased	**20 (2.9)**	17 (2.5)
Lipase increased	**12 (1.7)**	8 (1.2)
AST increased	**12 (1.7)**	7 (1.0)
Arthralgia	9 (1.3)	8 (1.2)
Back pain	**9 (1.3)**	7 (1.0)
Headache	**14 (2.0)**	8 (1.2)

Source: Table 14.3.1.3.4.3 Study Report

Less Common Adverse Events

Adverse events (on-treatment) which occurred in 1-2% telbivudine-treated patients included palpitations (1.3%), abdominal discomfort (1.3%), GERD (1.8%), hemorrhoids (1.2%), lethargy (1%), pain (1%), hepatic pain (1%), hepatitis B (1.3%), urinary tract infection (2.4%), gastroenteritis (1.9%), pharyngitis (1.5%), sinusitis (1.2%), tonsillitis (1.2%), increased amylase (1.3%), increased lipase (1.5%), increased ALT (1.3%), decreased weight (1.6%), decreased appetite (1.0%), pain in extremity (1.6%), neck pain (1.3%), musculoskeletal chest pain (1.2%), hypoaesthesia (1%), dysgeusia (1.2%), rhinorrhea (1.9%), rhinitis (1.5%), allergic rhinitis (1%), acne (1.9%), eczema (1%), urticaria (1%). Other less common, but significant adverse events in the telbivudine treatment group such as myopathy and myositis have been discussed above.

Medical Officer Comments: *No cases of lactic acidosis, hepatic steatosis, hepatomegaly or rhabdomyolysis were identified in the adverse event dataset for this study. There was one case of pancreatitis (Grade 1) in a patient who received telbivudine. In this case the event was described as mild, self-limited pancreatitis, and telbivudine was not discontinued or interrupted.*

Laboratory Findings

New-onset laboratory abnormalities were defined as laboratory values with increased toxicity grades in comparison to baseline value. If a patient experienced > 1 grade laboratory abnormality during the time period analyzed, the one with the maximum grade toxicity was summarized. From baseline to end-of-study (week 104),160/687 (23.3%) lamivudine recipients and 159/687 (23.4%) experienced a new-onset Grade 3 or 4 laboratory abnormality; while from after week 52 to the end-of-the study, 77/687 (11.2%) lamivudine and 92/680 (13.5%) telbivudine recipients experienced a new-onset Grade 3 or 4 laboratory abnormality. As shown in the following table over the entire study period, Grade 3 or 4 CK elevations were more common among telbivudine patients; and Grade 3 or 4 ALT, AST and lipase elevations were more common in lamivudine patients. A similar pattern of laboratory abnormalities was observed in the post-week 52 time period.

Table 51. New-Onset Grade 3 or 4 Laboratory Abnormalities

Laboratory Test	Lamivudine N=687	Telbivudine N=680	Lamivudine N=687	Telbivudine N=680
	All visits	All Visits	Week > 52-104	Week > 52-104
Any Grade 3/4	160 (23.3)	159 (23.4)	77 (11.2)	92 (13.5)
ALT	80 **(11.6)**	43 (6.3)	43 **(6.3)**	21 (3.1)
Amylase	3 (0.4)	1 (0.1)	1 (0.1)	0
AST	61 **(8.9)**	41 (6.0)	33 **(4.8)**	24 (3.5)
CK	28 (4.1)	88 **(12.9)**	9 (1.3)	56 **(8.2)**
Hemoglobin	2 (0.3)	0	2 (0.2)	0
Lipase	32 **(4.7)**	17 (2.5)	14 **(2.0)**	9 (1.3)
Neutrophils, absolute	14 (2.0)	14 (2.1)	5 **(0.7)**	1 (0.1)
Platelets	5 (0.7)	5 (0.7)	1 (0.1)	2 (0.3)
PT	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Total bilirubin	2 (0.3)	1 (0.1)	0	1 (0.1)

Source: 14.3.1.4.1.2 Study Report

Medical Officer Comments: *When the laboratory datasets were searched, 1 patient (007-016-012) who had Grade 3 and 4 ALT and AST elevations also had concomitant bilirubin (total) elevation to Grades 3 and 4 at Week 76, (verified by repeat laboratory analysis). This patient prematurely discontinued treatment at that time. No patients in the lamivudine treatment group had concomitant Grade 3 or 4 total bilirubin and ALT elevations. Concomitant elevations in the hepatic transaminases and total bilirubin may indicate drug-induced liver injury. However, in patients with underlying liver disease, particularly in patients with viral hepatitis, in whom compensated liver disease may progress to cirrhosis and/or liver failure, the liver injury could be attributed to either the underlying viral hepatitis or to an adverse drug effect. In this case, search of the adverse events dataset revealed that this patient experienced an increase in HBV DNA, increased alpha fetoprotein, jaundice and hepatic failure in the weeks prior to or at the same time as the ALT, AST and bilirubin elevations. Thus, in this case, the etiology of*

concomitant transaminase and bilirubin elevation was likely due to treatment failure and subsequent liver failure.

New Onset Grade 1 or 2 Laboratory Abnormalities

New-onset on-treatment Grade 1 or 2 laboratory abnormalities were reported in a majority of patients in both treatment groups, 622/687 (90.5%) lamivudine and 640/680 (94.1%) telbivudine patients. As shown in the following table, the most common Grade 1 or 2 laboratory abnormality in both treatment groups was increased CK, but this abnormality was more frequent in the telbivudine group (449/680, 66%) than the lamivudine group 310/687 (45%). Grade 1 or 2 AST and ALT elevations or increased creatinine were also more common in the telbivudine group; while increased lipase, decreased WBC, and < decreased absolute neutrophil count were more common in the lamivudine group.

Table 52. New-Onset Grade 1 or 2 Laboratory Abnormalities

Table 12-18 Summary of new-onset, on-treatment Grade 1/2 laboratory abnormalities from Baseline to End of Study, by treatment – overall Safety population

	Lamivudine (N=687)		Telbivudine (N=680)	
Laboratory Test	**n**	**(%)**	**n**	**(%)**
Albumin	9	(1.3)	5	(0.7)
ALT	266	(38.7)	283	(41.6)
Amylase	139	(20.2)	141	(20.7)
AST	276	(40.2)	312	(45.9)
CK	310	(45.1)	449	(66.0)
Creatinine	27	(3.9)	38	(5.6)
Hemoglobin	5	(0.7)	8	(1.2)
Lipase	137	(19.9)	114	(16.8)
ANC	80	(11.6)	56	(8.2)
Platelet count	32	(4.7)	40	(5.9)
Protein	56	(8.2)	61	(9.0)
Prothrombin time	133	(19.4)	117	(17.2)
Total bilirubin	87	(12.7)	86	(12.6)
WBC	27	(3.9)	24	(3.5)

Source: Table 12-18 NV-02B-007 Study Report

Medical Officer Comments: *The proportion of patients with new-onset Grade 1 or 2 CK elevations, ALT increases, AST increases, creatinine increase, and decreased platelets was higher in the telbivudine than the lamivudine treatment arm.*

Analyses of central tendency for changes in laboratory parameters were performed by the applicant. Changes in selected hematologic parameters from baseline to Week 104 are shown in the following table.

Table 53. Change from Baseline to Week 104 in Selected Hematologic Parameters

Hematologic Parameter	Statistical	Lamivudine	Telbivudine
WBC (x $10^3/\mu L$)	N	584	608
	Mean (SE)	0.17 (0.05)	0.12 (0.06)
	Median Range (min, max)	0.10 (-5.0, 5.5)	0.20 (-7.1, 5.6)
Hematocrit (%)	N	581	607
	Mean (SE)	-0.10 (0.12)	-0.41 (0.11)
	Median Range (min, max)	0.00 (-1.09, 0.62)	0.00 (-7.6, 0.63)
Hemoglobin	N	585	610
	Mean (SE)	0.08 (0.04)	-0.01 (0.03)
	Median Range (min, max)	0.00 (-3.8, 6.8)	0.00 (-2.3, 4.2)
Platelets (x $10^3/\mu L$)	N	578	601
	Mean (SE)	27.0 (1.4)	32 (1.5)
	Median Range (min, max)	27 (-169, 154)	30 (-130, 268)
Absolute Neutrophil Count (x $10^3/\mu L$)	N	584	607
	Mean (SE)	0.300 (0.048)	0.341 (0.054)
	Median Range (min, max)	0.240 (-4.06, 5.89)	0.400 (-6.53, 6.38)

Source: Tables 12-16, 14.3.1.4.3.1, and 14.3.1.4.9, NV-02B-007 Study Report

Medical Officer Comments: *Although the means and median change from baseline do not appear significantly different between treatment groups for hematological parameters, this type of analysis can mask large differences which occur in small numbers of patients.*

Changes from baseline in selected blood chemistry parameters are shown in the following table.

Table 54. Changes in Selected Chemistries from Baseline to Week 104

Table 12-16 Change from Baseline to Week 104 in blood chemistries – overall Safety population

Laboratory test	Lamivudine	Telbivudine
AST (IU/L)		
N	597	624
Mean (SE)	-53.5 (3.1)	-48.7 (2.9)
Median	-31.0	-30.0
25%, 75%	-75.0, -12.0	-66.0, -13.0
Min, max	-521, 231	-529, 598
Albumin (g/dL)		
N	598	624
Mean (SE)	0.18 (0.01)	0.21 (0.01)
Median	0.20	0.20
25%, 75%	0.00, 0.40	0.00, 0.40
Min, max	-1.0, 2.1	-0.7, 1.1
Amylase (U/L)		
N	598	624
Mean (SE)	-3.5 (2.3)	-2.6 (1.0)
Median	-1.0	-2.0
25%, 75%	-11.0, 8.0	-11.0, 6.0
Min, max	-1270, 143	-412, 76
Lipase (U/L)		
N	598	623
Mean (SE)	0.8 (0.9)	-1.0 (1.1)
Median	1.0	-1.0
25%, 75%	-4.0, 6.0	-6.0, 5.0
Min, max	-418, 124	-544, 254
Creatinine (mg/dL)		
N	598	624
Mean (SE)	-0.03 (0.01)	-0.10 (0.01)
Median	0.00	-0.10
25%, 75%	-0.10, 0.10	-0.20, 0.00
Min, max	-0.6, 0.6	-0.8, 0.6
Total bilirubin (mg/dL)		
N	593	624
Mean (SE)	-0.02 (0.01)	-0.01 (0.01)
Median	0.00	0.00
25%, 75%	-0.20, 0.20	-0.20, 0.20
Min, max	-1.1, 1.4	-1.5, 1.2

Source: Table 12-16 NV-02B-007 Study Report

Medical Officer Comments: *Minimal mean or median change from baseline was observed for total bilirubin, creatinine, lipase, amylase, and albumin in either treatment group. However, mean and median AST decreased more in the lamivudine than the telbivudine treatment group.*

In HBeAg-positive patients, the median change in ALT from baseline to week 104 was -73 IU/L (range -154, -28) in the lamivudine treatment group (n=463), and -78 IU/L (range -1089, 525) in the telbivudine group (n=458). In HBeAg-negative patients, the median change in ALT from baseline was -68.0 (range -961, 163) in lamivudine treated patients (n=224), and -68.5 (range -552, 1156) in telbivudine-treated patients. The median increase for CK from baseline to week 104 in the overall safety population was 8.0 IU/L(range -2696, 2368) among 598 lamivudine treated patients and 57.5 IU/L (range -2860, 3232) among 624 telbivudine treated patients.

Medical Officer Comments: *Note that for AST, ALT and CK, there was a significant range of values for change from baseline to week 104, underlying the limitation of this type of analysis. However, the higher median CK change from baseline in the telbivudine group is consistent with the known safety profile of telbivudine.*

Vital signs
When mean pulse, systolic and diastolic blood pressure results were analyzed, no significant change from baseline was noted for either treatment group from baseline to end-of-study.

ECGs
Electrocardiograms were not performed in this study.

Discussion of Safety Findings in Study 007
The proportion of patients who experienced at least one adverse event in this study increased from the first to the second year of the study in both treatment groups. The most common adverse events in both treatment groups were upper respiratory tract infection and nasopharyngitis. The common adverse events (> 3%) more frequent in the telbivudine than the lamivudine group included upper respiratory tract infection, nasopharyngitis, fatigue, increased blood creatine phosphokinase (CK), post-procedural pain, cough, diarrhea, nausea, rash, back pain, pyrexia, and myalgia.

The proportion of patients who discontinued treatment due to adverse events was similar in the lamivudine and telbivudine treatment groups. Adverse events resulting in treatment discontinuation more common in the telbivudine than lamivudine group included diarrhea, nausea, fatigue, increased CK, myalgia, and myopathy.

Creatine kinase (CK) elevations of any grade were more common in the telbivudine treatment group. Grade 3 or 4 CK elevations were reported in 4% lamivudine patients compared to 13% telbivudine patients. Increases in CK were most often asymptomatic, but a higher proportion of Grade 3 or 4 CK elevations in the telbivudine-treated patients occurred in association with a muscle-related adverse event or within 30 days of a muscle-related adverse event in comparison to lamivudine-treated patients. Median Grade 3 or 4 CK elevations peaked at approximately Week 52 and remained constant through Week 104 among telbivudine recipients.

Myopathy and myositis were reported as adverse events in 4/680 (0.6%) telbivudine-treated patients in this study, and peripheral neuropathy (polyneuropathy) was reported in 2/680 (0.3%) patients. ALT flares on-treatment were more common among lamivudine than telbivudine-treated patients, but in the 4 months post-treatment for patients who did not enroll in the follow-on study, 022, 8% of telbivudine and 5% of lamivudine recipients experienced an ALT flare. No cases of lactic acidosis, hepatic steatosis, or rhabdomyolysis were reported in this study.

Overall, no new safety signals were identified with review of the 104 week or overall safety data in this study.