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APPLICATION NUMBER:

22-011

MEDICAL REVIEW

CLINICAL REVIEW

Application Type: NDA
Submission Number: 22-011
Submission Code: 000

Letter Date: 2005-12-30
Stamp Date: 2005-12-30
PDUFA Goal Date: 2006-10-30

Reviewer Name: Charlene A. Brown, MD, MPH
Review Completion Date: 2006-10-25

Established Name: Telbivudine
(Proposed) Trade Name: Tyzeka™
Therapeutic Class: Nucleoside Analogue
Applicant: Idenix Pharmaceuticals

Priority Designation: S

Formulation: 600 mg tablets
Dosing Regimen: 600 mg once daily
Indication: Treatment of Chronic Hepatitis B Infection
Intended Population: Adults

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Medical Officer recommends the approval of telbivudine (LdT) for the treatment of chronic Hepatitis B Virus (HBV) in subjects with compensated liver disease and evidence of active liver inflammation by either elevated liver transaminases or liver biopsy. This recommendation is based on review of the efficacy and safety data submitted by Idenix Pharmaceuticals for this New Drug Application (NDA). There were not any significant inadequacies identified in the NDA that would preclude approval of LdT.

Several issues have been considered in determining the overall risk-benefit assessment of LdT in the treatment of chronic HBV and how LdT might fit into the current HBV treatment armamentarium. Chronic HBV plays a contributing role in the development of cirrhosis, hepato-cellular carcinoma (HCC), and mortality worldwide. Among subjects receiving study drug for 52 weeks in the pivotal, Phase 3 registrational trial, NV-02B-007, LdT resulted in reliable drug exposure in human subjects, no known significant drug-drug interactions, reduced HBV viral load, normalization of liver enzymes, and improvement in liver histology on a scale that was approximately equivalent to that achieved with lamivudine (LAM). Importantly, LdT was non-inferior to LAM in the achievement of the primary efficacy endpoint, Therapeutic Response[1], and the principal secondary efficacy endpoint, Histologic Response[2], among both HBeAg-positive and HBeAg-negative nucleoside-naïve adult subjects with chronic HBV. For the primary efficacy endpoint, Therapeutic Response, LdT was non-inferior to LAM in Asians and Other Races in both HBeAg subpopulations and Caucasians who were HBeAg-Negative. There were few non-Asians and non-Caucasians in the pivotal trial, however, limiting this Medical Reviewer's ability to interpret treatment effects that might possibly be linked to ethnicity. The Applicant will be asked to conduct an additional safety and efficacy study among select racial/ethnic groups (African-Americans and Hispanics) that were underrepresented in the pivotal trial.

The general tolerability and safety profile of LdT was similar to that of LAM over the observed dosing periods, with the exception of a higher rate of CK elevations and the occurrence of an infrequent, but significant drug-associated myopathy with muscle weakness. Assessment of the drug's safety and efficacy in dosing beyond 52 weeks is continuing in the ongoing clinical trials.

These positive findings from the LdT studies must be weighed against findings that are less clearly understood. LdT was unable to achieve non-inferiority when compared to LAM for HBeAg-positive subjects for the secondary efficacy endpoint of Change in Ishak Fibrosis Score. The interpretation of how LdT impacts HBV disease progression, as measured by fibrosis, should be

[1] Therapeutic Response was defined by the Applicant as attainment of serum HBV DNA < 5 $\log_{10}$ copies/mL linked with either HBeAg loss or ALT normalization.
[2] Histologic Response was defined as at least a 2-point reduction in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score.

tempered by the impact of LdT on other markers of clinical HBV outcomes, including TR and histologic response, where LdT met non-inferiority criteria.

Uncertainty also emerges in the assessment of the potential risk that LdT may cause a significant myopathy with associated muscle weakness in a subset of subjects. The features that increase risk for the development of this adverse event are not understood. Data derived from ongoing studies are expected to provide more information over time. Skeletal muscle warnings were agreed upon by both the FDA and the Applicant and included in the LdT label.

According to the clinical pharmacology findings reviewed by the FDA, after a radioactive oral 600mg dose of LdT, 91.6% of total dose was recovered in the urine (41.9%) and feces (49.6%) within 168 hours of dosing. LdT was excreted primarily in urine by passive diffusion, resulting in a low likelihood for interaction between LdT and other renally-excreted drugs. In addition, recommendations for dosing in renal failure were derived from clinical pharmacology studies of LdT among subjects with renal impairment. Dose adjustment was not found to be necessary among subjects with hepatic impairment.

In conclusion, the Phase 2 and Phase 3 LdT development program provided enough information on which to establish dose recommendation of 600mg once daily for nucleoside-naive adults with chronic hepatitis B, evidence of active liver inflammation by either elevated liver transaminases or liver biopsy, and compensated liver disease.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Although the Applicant did not submit a formal risk management plan, there are risk management activities planned for LdT after approval.

- As a required Phase 4, post-marketing commitment, the Applicant has agreed to submit the 104-Week data for the pivotal Phase 3 trial, NV-02B-007. These results will provide more safety data for analysis of existing or future LdT-associated toxicities.
- The Applicant will also submit periodic safety reports for review.
- The label includes Warnings language regarding the risk of lactic acidosis, hepatic steatosis, Hepatitis B exacerbation post-discontinuation of therapy, and skeletal muscle symptoms in an effort to minimize the risk/benefit ratio associated with the use of this product.
- The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product.
- The Division will continue discussions with the Applicant to ensure that a standardized management approach is implemented for all of subjects who develop CK elevations and/or muscle-related symptoms in the ongoing and future LdT clinical studies. The development of a systematic approach, which will be required by protocol, will better enable the systematic collection of the same categories of information across studies to allow better characterization of LdT-associated myopathy. The Applicant has agreed and is planning to

solicit feedback from several experts with the necessary background and expertise to develop the most medically appropriate algorithm and/or approach.

- This approach should include a protocol-specified definition for the types of clinical scenarios (e.g. CK elevation of any level with muscle weakness) that should trigger a specific algorithm for clinical, laboratory and other analyses.
- The algorithm should outline specific approaches based on symptom presentation (e.g. subjects with CK elevations and fatigue should not necessarily get a muscle biopsy) and may include full musculoskeletal exam including strength testing, urine myoglobin, CK, CK fractionation, EMG, muscle biopsy, etc.

Also, the Office of Surveillance and Epidemiology (OSE) has been briefed regarding the safety issues with this NDA submission at an NDA Safety Meeting held on September 25, 2006. If there are new or increased post-marketing safety signals, OSE will be consulted formally.

1.2.2 Required Phase 4 Commitments

The Applicant has agreed to conduct a series of post-marketing commitments designed to provide additional information on the durability of response to LdT treatment and the efficacy, and safety of LdT in additional key subject populations.

During a labeling teleconference on October 12, 2006, the Applicant was notified that this NDA, as an application for a new molecular entity, would be required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. In the original NDA submission, the Applicant proposed a general pediatric development plan and requested a parital waiver for conducting pediatric studies in the neonatal age group (ages 0 through 2 years). The Division is not granting a waiver for any pediatric studies at this time. The Applicant understands that the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) will be outlined in a Written Request for pediatric exclusivity subsequent to the action date for this NDA submission and will be considered required postmarketing study commitments.

Under the Pediatric Research Equity Act (PREA), the Division is deferring the following pediatric studies of LdT:

1. Deferred pediatric study/substudy under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.

2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 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.

The additional required Phase 4 commitments are described below:

Clinical

1. Complete and submit the final study report for Study NV-02B-007, the 104-Week, Phase 3 registrational trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with HBeAg-positive and HBeAg-negative chronic hepatitis B and compensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: July 2007

2. Conduct and submit a final study report to evaluate the use of LdT in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (blacks/African Americans, Hispanics).

   Protocol submission: June, 2007
   Final report submission: June 2010

3. Conduct and submit a final study report for an efficacy and safety study of telbivudine in subjects who are coinfected with HIV and HBV. This study should include analysis of virologic, biochemical, and serologic endpoints for both HIV and HBV. It should also include evaluation of safety, and evaluation of HBV and HIV resistance.

   Protocol submission: June, 2007
   Final report submission: June 2010

4. Complete and submit the final study report for Study NV-02B-011, the double-blind trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with chronic hepatitis B and decompensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: April 2010

5. Complete and submit the final study report for Study NV-02B-018, the open-label trial comparing the efficacy and safety of telbivudine to adefovir dipivoxil in subjects with HBeAg-positive compensated chronic hepatitis B.

   Protocol submission: Study Ongoing
   Final report submission: June 2007

6. Complete and submit the final study report for Study NV-02B-022, the open-label, non-comparative trial assessing the long-term antiviral efficacy and safety of telbivudine in subjects with HBeAg-positive and HBeAg-negative compensated and decompensated chronic hepatitis B that have been previously treated in Idenix-sponsored telbivudine studies.

   Protocol submission: Study Ongoing
   Final report submission: May 2012

Clinical Pharmacology

7. Conduct and submit a final study report for a study evaluating CYP induction potential for telbivudine using in vitro or in vivo studies.

   Protocol submission: January 2007
   Final report submission: January 2008

8. Conduct and submit a final study report(s) for in vitro studies to evaluate if telbivudine is a P-gp inhibitor.

   Protocol submission: January 2007
   Final report submission: January 2008

Microbiology

9. Conduct and submit a final study report for a study to determine the anti-HBV cell culture combination activity relationships of telbivudine with entecavir.

   Protocol submission: December 2006
   Final report submission: April 2007

10. Conduct and submit a final study report for a study to determine the anti-HBV combination activity relationships of telbivudine in cell culture with the HIV NRTIs abacavir, emtricitabine, lamivudine, tenofovir, zalcitibine, and zidovudine.

    Protocol submission: February 2007
    Final report submission: November 2007

11. Conduct and submit a final study report for a study to determine the susceptibility to telbivudine and adefovir of the HBV rtA181 variants, rtA181T and rtA181S.

    Protocol submission: Study Ongoing
    Final report submission: November 2007

12. Conduct and submit a final study report for a study to determine the susceptibility in cell culture of HBV harboring the following mutations of highly conserved amino acid residues among HBV isolates: R22C, W58G, L69P, L82M, P99L, L180M, L209V, T240I, I254F, P261L, G295E, A307V, L331F, or A342T. These amino acid substitutions were found in the viruses of patients who experienced virologic failure (serum HBV DNA levels ≥1,000 copies/mL at Week 52) to telbivudine therapy.

    Protocol submission: February 2007
    Final report submission: February 2008 and December 2009

13. Conduct and submit a final study report for a study to determine the mitochondrial toxicity of telbivudine in growing muscle cells, cell lines and primary cells, and primary hepatocytes with appropriate controls to validate the results.

    Protocol submission: March 2007
    Final report submission: March 2008

14. Complete and submit a final study report for ongoing genotypic and phenotypic analyses of

HBV DNA from patients who experience virologic failure to long-term telbivudine therapy (serum HBV DNA levels ≥1,000 copies/mL) in ongoing clinical trials.

Protocol submission: Study Ongoing (NV-02B-007)
Final report submission: July 2007 update for NV-02B-007 and then annually for those NV-02B-007 patients who roll-over to NV-02B-022 (July 2008 and July 2009).

1.2.3 Other Phase 4 Requests

Aside from the Phase 4 commitments listed above, no other recommended or optional Phase 4 commitments have been requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

LdT (Tyzeka™) is a new molecular entity (NME) in the nucleoside analogue class and, after phosphorylation to its active metabolite, is an inhiNbitor of HBV DNA polymerase. LdT 600mg once daily is indicated for the treatment of nucleoside- naive adults with chronic HBV with evidence of active liver inflammation and compensated liver disease. The various data generated by the Applicant during clinical trials of LdT were the primary sources of data for this clinical review. The primary source of clinical safety and efficacy data, however, was derived from Study NV-02B-007, the pivotal, randomized, double blind, LAM-controlled, Phase 3 clinical study of LdT in HBeAg-positive and HBeAg-negative subjects with chronic HBV and compensated liver disease. Additionally, data generated during the Phase 2b dose-finding study, NV-02B-003, and its follow-on study, NV-02B-010, were also reviewed, primarily for safety.

Additional safety data, albeit limited, were also available at the time of this NDA submission for several Phase 1 and Phase 2 studies. Data from Phase 1 and Phase 2 studies are mentioned as supportive evidence of the Phase 3 safety assessment. The overall safety database meets the requirements outlined in the FDA Guidance Documents and approximates the size of the safety database for previously approved anti-HBV drugs.

All clinical studies submitted with this NDA are listed below in Section 4.2, Table of Clinical Studies.

1.3.2 Efficacy

The Division of Antiviral Products (DAVP) Review Team concluded that in a well-conducted, multinational, pivotal Phase 3 study of subjects with compensated liver function, LdT was effective in the treatment of adults with chronic HBV infection and evidence of ongoing liver inflammation. The large Phase 3 study met the FDA criteria for an adequate and well-controlled study and had sufficient size to allow each of the two HBeAg subpopulations within the trial to serve, for analytical purposes, as separate trials.

According to the statistical testing procedures agreed upon by the Applicant and the Division, the superiority of LdT over LAM was demonstrated in the HBeAg-positive subpopulation for the primary efficacy endpoint, Therapeutic Response, as well as Histologic Response, Serum HBV DNA Reduction and Serum HBV DNA Undetectable. However since superiority for the same endpoints was not demonstrated in the HBeAg-negative subpopulation, DAVP will require replication of the superiority findings in the HBeAg-positive subgroup in another study before allowing the Applicant to make a superiority claim in the label.

Non-inferiority of LdT to LAM was also demonstrated in the HBeAg-positive subpopulation for Virologic Response, HBeAg seroconversion and HBeAg Loss and in the HBeAg-negative subpopulation for Change in Ishak Fibrosis Score. Change in Ishak Fibrosis Score for LdT did not meet the pre-specified non-inferioritiy criterion for the HBeAg-positive subpopulation. This finding, although concerning, was tempered by the limitations of liver biopsy, and the more supportive findings of non-inferiority for other key efficacy endpoints, including Histologic Response, PCR non-detectable HBV DNA and Therapeutic Response.

As noted above in Section 1.1, LdT was non-inferior to LAM in Asians and Other Races in both HBeAg subpopulations and Caucasians who were HBeAg-Negative for the primary efficacy endpoint, Therapeutic Response. Interestingly, LdT seemed to have the most notable treatment effects (compared to LAM) in Asia. There were few non-Asians and non-Caucasians in the pivotal trial, however, limiting this Reviewer's ability to interpret treatment effects that might possibly be linked to ethnicity. Additionally, the non-inferiority of LdT relative to LAM was seen in males in both HBeAg subpopulations and females who were HBeAg-Positive.

The non-inferiority of LdT to LAM was established in both HBeAg subpopulations for Therapeutic Response (the primary endpoint), Histologic Response, (the primary secondary endpoint), Serum HBV DNA Reduction, Serum HBV DNA Undetectable, ALT Normalization and Virologic Breakthrough at Week 48. There are limitations to the efficacy data presented in the LdT NDA, however. As noted earlier, the small number of blacks/African Americans and Hispanics enrolled in the clinical development program did not provide sufficient evidence to determine whether they may be a different treatment effect. Also, there were some possible treatment effect questions raised by the subgroup analsyses within the HBeAg-negative subpopulation. These questions may also be related to the small numbers of female subjects. In addition, data is not yet available to draw conclusions about the efficacy of LdT in patients with decompensated liver disease, although a relevant study, NV-02B-011, is ongoing.

The microbiology resistance analyses, based on review by FDA virologists, suggest that LdT is unlikely to work in most subjects with LAM resistance (rtM204I or rtL180M/rtM204V). While LdT retained *in vitro* susceptibility to rtM204V alone, this mutation is not usually found in isolation among LAM-resistant patients. The findings also suggest that LdT is unlikely to be effective in subjects with adefovir dipovoxil (ADV) resistance (rtA181V) because LdT is 3 to 5 times less affective against this mutation, but clinical experience will reveal whether or not LdT may have a role for subjects with ADV resistance due to the rtN236T substitution. Since entecavir (ETV) - associated resistance substitutions have emerged when LAM-resistant mutations at L180 and/or

M204 are present, LdT is unlikely to retain efficacy among patients with ETV resistance because those patients will also have underlying LAM-resistant mutations.

Finally, although the results of these studies support the non-inferiority of LdT treatment compared to LAM treatment by a variety of histologic, serologic, virologic, and composite endpoints measured at 52 weeks, there are no data comparing LdT to ADV or ETV for the treatment of chronic HBV, although a comparison study with ADV is underway.[3]

1.3.3 Safety

The safety profile of LdT was similar to that of LAM in pivotal Phase 3 trial, with the exception of creatine kinase (CK) elevations and myopathy among LdT subjects and late alanine aminotransferase (ALT) flares among LAM subjects. The pattern of commonly reported adverse events (AEs) was relatively high with 75% of LdT subjects and 71% of LAM subjects reporting at least one AE.

If all AEs of any intensity are considered, the most commonly reported events in LdT-treated subjects included: upper respiratory infection, fatigue/malaise, nasopharyngitis, headache, creatine phosphokinase (CPK)[4] increased, abdominal pain, and cough. Many of these events are common in the general population and in the population of patients with chronic HBV.

Four categories of events deserved increased attention because of signals from animal toxicology or the potential seriousness of the adverse events. Among these, only CK elevations and myopathy with muscle weakness have been shown to occur more frequently among LdT-treated subjects to date.

ALT flares have been described during treatment with all of the approved drugs for chronic HBV and after discontinuation of drugs that have activity against HBV. ALT flares were documented infrequently in subjects during the on-treatment period but occurred more often in subjects receiving LAM; 3% of LdT-treated subjects and 5% of LAM -treated subjects experienced a flare, based on American Association for the Study of Liver Diseases (AASLD) flare criteria. ALT flares more commonly resulted in study drug discontinuation among LAM subjects than LdT subjects. There were very little limited data to estimate the risk of hepatitis B exacerbation after treatment discontinuation; however, the available data do suggest that persons who discontinue therapy may be at increased risk for post-treatment flares, relative to persons who start another form of anti-HBV treatment.

The finding of CK elevations among subjects on LdT was of particular interest during the review. Possible LdT-associated CK elevations were identified during the Phase 2b study, NV-02B-003, and the pivotal trial, NV-02B-007. In the pivotal trial, CK elevations occurred in both treatment arms; however median CK levels were higher in LdT-treated subjects by Week 52. Grade 1-4 CK elevations occurred in 72% of LdT-treated subjects and 42% of LAM-treated subjects, whereas Grade 3/4 CK elevations occurred in 9% of LdT-treated subjects and 3% of LAM-treated subjects. Although most CK elevations were asymptomatic, 8% of LdT subjects (compared to 6% of LAM

[3] Study NV-02B-018 is a randomized, open label trial of LdT versus ADV in adults with HBeAg-Positive, compensated chronic HBV.
[4] The terms CK and CPK are used interchangeably in this review.

subjects) experience a CK-related AE[5] (within a 30-day window). Furthermore, 9% (5/55) of the LdT-treated subjects with a CK-related adverse event interrupted or discontinued study drug to the adverse event; these subjects recovered after study drug discontinuation or interruption. Less than 1 % of LdT-subjects overall were diagnosed with myopathy with muscle-weakness; those subjects who discontinued study drug recovered. There have not been any known clinical cases of rhabdomyolysis, with or without renal failure, in the LdT development program.

There seems to be an emerging, but infrequent pattern of a cumulative, toxicity resulting in myopathy, including muscle weakness, for a subset of subjects on LdT. To date, the myopathy has occurred with LdT use greater than 8-10 months. No subjects on LAM have yet discontinued or interrupted study drug due to an adverse event related specifically to muscle weakness in either the Chinese (NV-02B-015) or American (NV-02B-007) LdT registrational trials.

The mechanism of LdT muscle toxicity remains unclear. There has also been insufficient data to determine whether or not the subjects who developed drug-associated myopathy share one or more common predisposing risk factors. Continued evaluation of LdT-associated CK elevations and muscle symptoms will occur in the ongoing LdT trials as described above in Section 1.2.1.

There was preclinical spinal cord and sciatic axonopathy among monkeys in all LdT dose groups (including controls). The presence of these findings in control animals suggests that they are not LdT-associated. In the pivotal clinical study, rates of sensory-related AEs were evaluated and found to be similar across treatment groups. A significant pattern of LdT-related sensory AEs was not found. Of note, one LdT subject in the Phase 2b study developed a peripheral neuropathy requiring study drug discontinuation. Ongoing studies will provide additional data.

The highest LdT dose group among Sprague-Dawley rats had a higher rate of mortality due to chronic progressive nephropathy (CPN), raising questions regarding the role of LdT in the development of this renal toxicity. In clinical studies with LdT, there was no evidence for a pattern of LdT-associated nephropathy in the Phase 1 and 2 trials or the Phase 3 registrational trial. Only one case of nephrotic syndrome in an LdT-treated subject has been reported and that subject had multiple pre-existing risk factors (diabetes mellitus, hypertension, baseline proteinuria). Based on current evidence, it seems unlikely that LdT worsens renal function in subjects with chronic hepatitis B and normal renal function. It is possible, however, that as more subjects with chronic hepatitis B and compromised renal function or a high risk for compromised renal function (e.g diabetes, hypertension, elderly, etc.) initiate treatment with LdT, an adverse event profile of nephropathy may emerge.

High LdT doses led to some gastrointestinal (GI) intolerance in pregnant rabbits, non-pregnant monkeys, and rats. One pregnant rabbit died at the 1000 mg/kg/day dose, while two had premature deliveries and one aborted. The death occurred after more than 10 doses of LdT; hence GI irritation could be a dose limiting toxicity in rabbits. The AUC value in the pregnant rabbits at 1000 mg/kg/day, however, was 37 times higher than that in humans. While approximately 30% of subjects in the pivotal clinical trial experienced at least one adverse event (AE) in the Gastrointestinal Disorders System Organ Class (SOC), the rate of occurrence of these AEs was equal between the treatment arms (30% LdT and 30% LAM). GI toxicity is unlikely to be dose limiting in humans. It is unknown, however, whether or not patients with pre-existing gastrointestinal disease or patients who experience a significant LdT overdose may be at risk for

[5] Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, and pain in extremity.

significant GI toxicities.

1.3.4 Dosing Regimen and Administration

The data provided in the LdT NDA support the approval of LdT for the treatment of chronic HBV at a dose of LdT 600 mg once daily in nucleoside-naïve adult patients with compensated liver disease and evidence of active liver inflammation. The results of the pivotal Phase 3 study support this dose and the once daily dosing interval has also been validated by the PK data.

The pharmacokinetics of LdT are not significantly affected by gender, race and hepatic impairment, but are affected by renal impairment. Dose adjustment based on renal impairment has been recommended by the Applicant, but was not found to be necessary among subjects with hepatic impairment. In the population PK analysis, LdT steady-state PK were predicted for Caucasian, African American, and Asian subjects, revealing no significant differences between the subjects in these categories. Dose adjustment based on race, age, or gender is not recommended. In addition, based on the PK results for heavy-weight subjects in NV-02B-001, clinically significant differences in efficacy based on weight were not expected. Dose adjustment based on weight is not recommended.

Additionally, food effect studies suggest that LdT may be taken on an empty stomach or with food. LdT may be dosed with or without food.

1.3.5 Drug-Drug Interactions

There was no alteration of LdT PK with LAM, ADV, cyclosporine and pegylated interferon-alfa 2a in drug-drug interaction studies. In addition, LdT does not alter the PK of LAM, ADV, or cyclosporine. It was not possible to draw definitive conclusions regarding the effects of LdT on the PK of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.

In addition, LdT demonstrated low plasma protein binding (3.3%). Given that the estimated apparent volume of distribution is in excess of total body water, LdT appears to be widely distributed after oral administration. After a radioactive oral 600mg dose of LdT, 91.6% of total dose was recovered in the urine (41.9%) and feces (49.6%) within 168 hours of dosing. LdT was excreted primarily in urine by passive diffusion, resulting in a low likelihood for interaction between LdT and other renally-excreted drugs.

LdT was not metabolized in humans. In addition, LdT was not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system based on an *in vitro* study. While an animal study showed that LdT was not an inducer of CYP enzymes, it remains unknown whether or not LdT is an inducer of CYP enzymes in humans.[6] It is not known if LdT is a substrate for the transporter P-glycoprotein because a positive control (digoxin) was not included in the study. Also, the potential for LdT to inhibit P-glycoprotein was not evaluated.

[6] No *in vitro* studies in human hepatocytes or *in vivo* human studies has been conducted to show telbivudine is not an inducer of CYP enzymes.

1.3.6 Special Populations

The Applicant evaluated LdT exposure in subjects with renal impairment (including those requiring hemodialysis). Following a single 200 mg dose of LdT, a 4-hour hemodialysis session removed approximately 23% of the LdT dose within 2 hours of the dose. Based on simulations performed to assess the effects of varying degrees of renal impairment on LdT PK, dose interval adjustments for subjects with renal impairment were proposed by the Applicant and accepted by the Agency. The Agency prefers dose reduction over dose interval adjustment, however, given the overall acceptable safety profile associated with LdT 600mg, the dose adjustment proposed by the sponsor is acceptable until the Applicant

Studies have not been conducted in HIV/HBV co-infected subjects, LAM-refractory subjects, or in women who were pregnant or breastfeeding. It is expected that post-approval, LdT will be taken by women who may become pregnant or already be pregnant while receiving the drug. The Applicant is making arrangements to participate in the Antiretroviral Pregnancy Registry, a national registry for pregnant women who receive treatment for HIV. Several anti-HBV drugs have already been included in the registry (ETV, LAM, and ADV).

As noted above in Section 1.2.2, pediatric studies of LdT have not been conducted to date. Both the Agency and the Applicant agree that they should proceed with refining the LdT pediatric development plan. The Agency will submit a formal Pediatric Written Request to the Applicant.

further facilitating the development of pediatric studies for LdT.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Telbivudine (LdT) is a synthetic nucleoside analogue that has been developed for the treatment of adults chronically infected with hepatitis B virus (HBV). It is phosphorylated to its active metabolite, telbivudine-5'-triphosphate which then inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, deoxythymidine-5'-triphosphate. Incorporation of telbivudine-5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication.

Generic (trade) name: Telbivudine (TYZEKA™), abbreviated as LdT throughout this review
Chemical class: New molecular entity
Pharmacological class: Nucleoside analogue, inhibitor of HBV DNA polymerase
Proposed indication: treatment of chronic HBV in nucleoside-naive adults with evidence of active liver inflammation and compensated liver disease.
Dosing regimens: 600 mg once daily

Age groups: Adults and adolescents ≥ 16 years of age.

2.2 Currently Available Treatment for Indications

At present, there are 5 approved treatments for chronic HBV infection marketed in the United States: entecavir, interferon-alpha, lamivudine, and adefovir dipivoxil.

Interferon-alpha (IFN) is a naturally-occurring cytokine that acts as an immune modulator that was approved for the treatment of HBV in 1992. It requires parenteral administration and has a side effect profile that includes flu-like symptoms, fever, malaise, myalgias, and autoimmune disorders.

Pegylated Interferon-alfa2a is a covalent conjugate of recombinant alfa-2a interferon with a PEG moiety linked at a single site to the interferon alfa moiety. It was approved for the treatment of HBV in 2005. It also requires parenteral administration and has a side effect profile that includes flu-like symptoms, fever, malaise, myalgias, and autoimmune disorders

Lamivudine (LAM) is the first oral, nucleoside analogue approved for the treatment of HBV in 1998. It is well-tolerated but long-term use has resulted emergence of resistance in the HBV of patients taking the drug (See Section 2.4, Important Issues with Pharmacologically Related Products for more details on LAM resistance).

Adefovir dipivoxil (ADV) is an acyclic nucleotide phosphonate analogue that was approved for the treatment of HBV in 2002. Throughout this review, ADV is considered to be in the same class as nucleosides. ADV has been associated with dose-related renal toxicity, resulting in limited use of the drug among patients with chronic HBV and renal impairment and among those requiring other nephrotoxic drugs.

Entecavir (ETV) is an orally bioavailable nucleoside analogue with potent anti-HBV activity that was approved in the spring of 2005. In Phase 3 trials, ETV produced better HBV suppression, ALT normalization, and histologic responses compared to LAM in subjects with HBeAg-positive and HBeAg-negative chronic HBV. ETV use may be associated with potentially significant safety issues, including dose-related carcinogenicity in two animal species, potential teratogenicity, and CNS toxicities (headaches and visual disturbances) observed in a small study.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity (NME) and is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

As noted above in Section 2.2, two nucleoside analogues (LAM and ETV) and one nucleotide analogue (ADV) have been approved for the treatment of chronic HBV infection. In addition, nucleoside analogues used as HIV reverse transcriptase inhibitors (NRTIs) have also been a critical component of combination drug regimens for the treatment of HIV infection. Consequently, there

is a significant amount of safety experience with the use of this pharmacologic drug class among chronically ill patients.

Toxicity to human mitochondrial DNA, associated with NRTIs as a class, has been associated with adverse events including pancreatitis, lactic acidosis, peripheral neuropathy, myopathy and the fat redistribution syndromes. Compared with some of the other nucleoside analogues, these adverse effects appear to occur less frequently among patients taking LAM, ETV, and ADV.

There has also been the development of HIV cross-resistance with some of the NRTIs. Both LAM and ADV have activity against HIV and LAM was approved initially as an antiretroviral drug. LAM is cross-resistant with some of the other NRTIs.

With longer-term use of LAM, there has been the selection of resistant mutants, often affecting the YMDD motif of the HBV DNA polymerase. LAM resistance presents clinically as HBV breakthrough in up to 32% of patients after one year of treatment and up to 69% of patients after 5 years of treatment. ADV and LAM do not appear to be cross-resistant for HBV by *in vitro* assays and ADV has been used to suppress LAM-resistant HBV mutants clinically. In addition, ADV does not result in much resistance in the first year of therapy. Only 2.5% of HBeAg-negative patients with chronic HBV developed rtN236T mutation during the second year of therapy. This resistant mutant might be susceptible to LAM and ETV, based on *in vitro* data. *In vitro* data suggests that ETV is more potent than LAM and ADV.[7,8]

Other drugs used in HBV treatment trials, including tenofovir and emtricitabine have not been approved for the treatment of HBV infection. The role of combination therapy in the treatment of HBV infection remains unclear.

2.5 Presubmission Regulatory Activity

The first-in-man study of LdT was a blinded, dose-escalating, Phase 1/2a study assessing the safety and pharmacokinetics (PK) of LdT. It was submitted by Novirio Pharmaceuticals, Ltd. to the FDA under IND 60, 459; Serial No. 000 on May 31, 2000. At that time, LdT was assigned the generic name, epavudine, pending approval by the United States Adopted Name (USAN) Council. Subsequent drug development included pre-clinical testing and additional Phase 1 and Phase 2 studies, with the Division of Antiviral Products (DAVP) providing feedback on study design and populations, clinical endpoints, and safety monitoring.

Ultimately the generic name adopted by USAN (April 24, 2002) was telbivudine. The revised generic name was submitted to the FDA on May 31, 2002. In addition, the original IND sponsor, Novirio Pharmaceuticals, Ltd., changed its name to Idenix Pharmaceuticals, Inc. (Idenix).

On June 17, 2002, an End-of-Phase 2 meeting was held between Idenix and the Division of Antiviral Products to discuss the available safety and efficacy data from the completed/ongoing Phase 1-2 clinical studies and the proposed plan to initiate Phase 3 clinical trials in adult subjects

[7] Lok ASF, McMahon BJ. AASLD Practice Guidelines: Chronic Hepatitis B. Hepatology. 2001 Dec; 34(6): 1225–1241.
[8] Lok ASF, McMahon BJ. AASLD Practice Guidelines. Chronic Hepatitis B: update of therapeutic guidelines. Hepatology. 2004 Jun; 13(2): 150-4.

with chronic HBV. Specifically, the discussion resulted in the following agreements regarding Phase 3 study design:

- Combining HBeAg-positive and HBeAg-negative subjects in a single trial was acceptable.
- HBsAg-positive at screening with compatible histology was acceptable as an alternate definition of chronic HBV.
- The 600mg once daily dose of LdT was considered acceptable for Phase 3 studies.
- The results of liver biopsies at Year 1 should be included as part of the NDA.
- For the proposed composite primary efficacy endpoint, Therapeutic Response,[9] DAVP would obtain additional public and expert input at the planned August 7, 2002 HBV-directed Advisory Committee meeting.
- With additional supportive data, a single study, plus a small study in subjects with chronic hepatitis B and decompensated liver diease, was considered acceptable as the primary basis of approval.[10]
    - The Division outlined some of the risks involved in a single Phase 3 study, including a statistical risk from marginal efficacy results and the possibility that sample size might not be adequate to show differences due to race or geography.
    - A 15% delta for the non-inferiority, active-controlled, pivotal study was acceptable if histology was used as the primary efficacy endpoint and possibly acceptable if the proposed composite efficacy endpoint, therapeutic response, was used as the primary endpoint.
    - For a single combined Phase 3 trial, showing that the lower limit of the one-sided (100-0.125/2)=99.9375 confidence interval on the difference in response rates is greater than 0% may not be enough to make a superiority claim in the label for LdT over the comparator drug.

Primary Efficacy Endpoint

As planned, the possible use of a composite efficacy endpoint as the primary efficacy endpoint in future Phase 3 trials was discussed at length during the August 7, 2002 Antiviral Drugs Advisory Committee meeting on clinical-trial-design issues for drugs to treat chronic hepatitis B.[11] Some Advisory Committee members favored a composite endpoint (e.g. combination of virologic, biochemical and or serologic endpoints), while others advocated for maintaining the primacy of a primary histologic endpoint. The Committee acknowledged that neither a histologic endpoint nor a composite endpoint would be a perfect measure of efficacy and that neither has been proven to correlate with clinical outcome. There appeared to be consensus, however, among Committee members that the population being treated and the goals of therapy should, at least partially, influence the selection of the primary endpoint. The Agency was encouraged to remain cognizant of this and flexible in its selection of endpoints. The DAVP interpretation of the Hepatitis B Advisory Committee meeting was that consensus was not reached regarding whether or not

[9] Therapeutic Response was defined by the Applicant as attainment of serum HBV DNA < 5 $\log_{10}$ copies/mL linked with either HBeAg loss or ALT normalization.

[10] The Division ultimately did not require that the Applicant include the results of a small study conducted in decompensated subjects as a condition for submitting a single, large, pivotal study for registrational purposes since there was other supportive Phase 2 data. In a teleconference on March 4, 2002, the Division notified Idenix that a single Phase 3 study combining HBeAg-positive and HBeAg-negative subjects was acceptable. In addition, the Division noted that LdT was more likely to receive a standard review than a priority review at the time of NDA submission without the inclusion of study results in decompenasted subjects.

[11] Antiviral Drugs Advisory Committee Meeting Minutes, US Food and Drug Administration, Department of Health and Human Services, August 7, 2002.

histology should remain the primary endpoint for trials of anti-HBV drug products, due largely to the inconsistent correlations between histology and other surrogate endpoints.

As noted above, the Applicant initially proposed a novel, composite, primary efficacy endpoint, Therapeutic Response, but the Division preferred to use histologic response as the primary efficacy endpoint, initially due to the lack of public input and data supporting the use of a non-histologic primary endpoint. Subsequent to public and expert input garnered through the August 2002 HBV Advisory Committee meeting and continued communications with Idenix, the Division eventually accepted histologic response as an important secondary efficacy endpoint in written comments faxed to the Applicant on October 29, 2002. The Division noted that as long as paired histology specimens would be obtained from an adequate number of subjects, it was less important whether or not histology is a primary or secondary endpoint. In a teleconference between the Division and the Applicant the next day, both parties agreed that histology could be acceptable as an extremely important secondary efficacy endpoint, concurrent with an appropriate plan to obtain paired biopsy specimens from a significant majority of subjects (which were representative of the study demographics).

Consequently, the proposed composite, primary efficacy endpoint, Therapeutic Response, was selected for the LdT Phase 3 registrational trial. As noted by the Applicant in the NV-02B-007 protocol, the composite Therapeutic Response endpoint is conceptually related to the composite "Virologic Response" endpoint used in early interferon trials in HBeAg-positive subjects. Also, they noted that a composite serologic endpoint comprising HBV DNA suppression and ALT normalization had been used in several large clinical trials involving HBeAg-negative subjects with chronic hepatitis B. The three component composite endpoint designated as Therapeutic Response conceptually combines both types of composite efficacy endpoints used previously. It was proposed that subjects who obtained Therapeutic Response would both achieve the guideline-recommended degree of HBV DNA suppression (HBV DNA levels <5 log10 copies/mL, as recommended by the American Association for the Study of Liver Diseases (AASLD) and Asia Pacific Association for the Study of Liver (APASL) guidelines) together with either HBeAg loss or ALT normalization, two surrogate measures of clinical benefit that can be monitored in hepatitis B subjects with antiviral therapy. Therapeutic Response was not considered a treatment discontinuation endpoint. In HBeAg-negative subjects, the Therapeutic Response endpoint was driven only by the ALT and HBV DNA components.

Single Phase 3 Safety and Efficacy Study

As noted earlier in this section, the Division agreed that a single, large, Phase 3 study combining the two primary HBV subject populations (HBeAg-positive and HBeAg-negative) was acceptable for the LdT Phase 3 registrational trial. Other anti-HBV drugs have been approved based upon the safety and efficacy review of least two registrational trials, in which HBeAg-positive and HBe-Ag-negative subjects were studied separately (e.g. ADV, ETV). Given the large number of planned subjects (n=1200) for the LdT Phase 3 trial and the separate analyses planned for HBeAg-positive and HBeAg-negative subjects, the Division agreed to a single, large, Phase 3 study. Essentially, NV-02B-007 was designed to have a target study population and size equivalent to the study population and size usually associated with two registrational HBV treatment trials. Consequently, NV-02B-007 was a single study largely for administrative purposes. Specific analysis and other considerations were also necessary for the Division to accept a single Phase 3 registrational study.

Due to possible inconsistencies in the treatment effects across the two target populations (HBeAg-positive and HBeAg-negative) and the slight differences in the therapeutic response endpoints beween the two target populations, a combined analysis was considered problematic. A separate

analysis was required including stratification by HBeAg status, baseline ALT and other randomization stratification variables.

Subsequent to the approval of adefovir (ADV) for the treatment of chronic Hepatitis B on September 20, 2002, a placebo-controlled long-term study of chronic HBV treatment would have been considered unethical at the time that the LdT Phase 3 trial was being designed. During the June 17, 2002 End-of-Phase 2 Meeting, the Division and Idenix discussed the difficulties associated with a placebo-control design and agreed that an active-control design was acceptable for NV-02B-007.

Since LAM was the only approved drug for the treatment of chronic hepatitis B until adefovir (ADV) was approved on September 20, 2002, the Phase 3 trial was planned with LAM as the comparator drug. It would be possible to demonstrate that LdT was superior to LAM only if it was also proven that LAM was effective in this particular trial. Since it would not be possible to prove that LAM was effective in the LdT Phase 3 trial without the presence of a placebo, it was considered necessary to show that LdT was no worse than LAM (non-inferior) by a prespecified non-inferiority margin, delta, prior to any assessment of superiority.[12]

The Applicant reported that the non-inferiority margin has usually been calculated to be half the distance between response rates of the active control arm vs. placebo based on the scientific literature. With the proposed novel, composite primary efficacy endpoint, Therapeutic Response, there were no historical data. The Applicant estimated that the response rate for the Therapeutic Response would be 50% for LAM and 10% for placebo-treated subjects. With these assumptions, then half of the LAM effect over placebo was found to be 20%. The Applicant proposed a conservative difference of 15% as the minimum criterion for non-inferiority. The Division agreed that a 15% non-inferiority margin was reasonable for the Phase 3 registrational trial for both the histologic improvement and the Therapeutic Response efficacy endpoints. It was necessary, therefore, that the baseline characteristics for the LdT registrational trial not differ substantially from the LAM trials.

In the context of non-inferiority, subjects that remained in the study, but refused the end-of-study biopsy, were to be excluded from the primary analysis. In the context of superiority, subjects that refused the end-of-study biopsy were to be coded as treatment failures for the primary analysis. If the LdT treatment effect was consistent in both HbeAg-postive and HbeAg-negative sub-populations, it was to be evaluated in each sub-population using the 0.05 alpha levels. Otherwise it was to be evaluated at the 0.00125 level of significance in each HBeAg sub-population. Results for the primary analysis would have to be positive before statistical significance in HbeAg-positive and HbeAg-negative subpopulations would be considered.

The key concepts above were communicated to the Applicant via telephone facsimile on July 15, 2002 and eventual agreement on study design and analysis was reached between Idenix Pharmaceuticals and the Division over the ensuing months.

On April 5, 2005, a pre-NDA meeting was held between Idenix and the Division of Antiviral Products. Key points addressed during this meeting included anticipated format and content issues for eventual NDA submission[13] and requirements for Division consideration of the LdT NDA for a

[12] Chi GYH, Chen G, Liu K and Wang YC. "Active Control Non-Inferiority Trial-The Hypothesis." Presentation on November 1, 2004, BASS XI, Savannah, GA.

[13] The Clinical Pharmacology team expressed a preference for dose reduction in renally impaired subjects rather than dose interval adjustment due to increased PK fluctuations associated with interval adjustments.

Formulations: 600 mg film-coated tablets (oral administration) containing the following inactive ingredients; microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate and colloidal silicon dioxide. The tablet coating contains titanium dioxide, polyethylene glycol, talc and hypromellose.

[redacted]

As noted above in Section 2.5, Presubmission Regulatory Activity, LdT was assigned the generic name, epavudine, pending approval by the United States Adopted Name (USAN) Council, at the time of the original IND submission. Ultimately the generic name adopted by USAN was telbivudine.

Please refer to Dr. Ko-Yu Lo's CMC review for a detailed analysis of LdT's chemistry, manufacturing and controls.

3.2 Animal Pharmacology/Toxicology

Please refer to Dr. Ita Yuen's Animal Pharmacology/Toxicology Review for a detailed analysis of the LdT pharmacology and toxicology data. A summary of both the Applicant's findings and Dr. Yuen's findings are provided below.

The preclinical animal pharmacology/toxicology program included chronic toxicity and carcinogenicity studies in the mouse, rat, rabbit, cynomolgus monkey and woodchuck. These species were chosen due to the similarities that they share with human metabolism. All dosing was oral, the planned route of administration for humans. LdT did not change cardiovascular, CNS, respiratory or hemodynamic pharmacology at large multiples of exposure.

In general, LdT was found to be well tolerated and produced few or no adverse effects at large multiples of human exposure. In animal studies, LdT resulted in systemic exposures (AUC) approximately 8-fold (monkeys) and 14-fold (rats) the exposure levels observed in humans. Nevertheless, no LdT-related effects were found in hematology or serum chemistry parameters. High LdT doses led to some gastrointestinal (GI) intolerance in pregnant rabbits, non-pregnant monkeys, and rats. The rabbits gained less weight; the monkeys had occasional soft stools and vomiting, whereas the rats had only occasional symptoms. In addition to reduced body weight gain and abnormal feces, one pregnant rabbit died at the 1000 mg/kg/day dose. This rabbit showed evidence of gastrointestinal irritation, including reduced food consumption and less body weight gain, abnormal feces, erosion on the stomach mucosal surface, reddish fluid and appearance in the intestine, and distended stomach and intestine (with gas). The death occurred after more than 10 doses of LdT; hence GI irritation appears to be a dose limiting toxicity in rabbits. The AUC value in the pregnant rabbits at 1000 mg/kg/day was 2-3 times higher than those at the highest doses studied in mice, rats, and monkeys, and 37 times higher than that in humans. This toxicity is unlikely to be a dose limiting in humans. Unlike the pregnant rabbits and the rats, the mice did not demonstrate GI intolerance.

MO Comments
While approximately 30% of subjects in the pivotal clinical trial (NV-02B-007) experienced at least one adverse event (AE) in the Gastrointestinal Disorders System Organ Class (SOC), the rate of

occurrence of these AEs was equal between the treatment arms (30% LdT and 30% LAM). Only one subject on LdT (Subject # 005-007) in the pivotal trial discontinued study drug due to gastrointestinal adverse event (nausea and loose stool). The preclinical GI toxicity is concerning at high LdT exposures, however, since the AUC associated with this GI toxicity is 37-times higher than that in humans, it is unlikely to be dose limiting in humans. It is unknown, however, whether or not patients with pre-existing gastrointestinal disease or patients who experience a significant LdT overdose may be at risk for a more serious GI toxicity.

The Applicant noted that no consistent histopathologically confirmed damage to any tissue or organ could be attributed to LdT in the animal toxicity studies, despite myriad, sometimes confounded findings. Below are preclinical findings, raised by the Applicant, that merit more detailed discussion.

- Spinal cord and sciatic axonopathy was noted in all LdT dose groups (including controls) in monkey studies. The mechanism of axonal injury is unknown, particularly since the control primates also had similar lesions. In addition, there were more sciatic lesions in high dose (1000 mg/kg/day) female monkeys and more spinal axonapthic lesions in (1000 mg/kg/day) male monkeys. The Applicant solicited independent pathology reviews, but neither the independent pathologist nor the study pathologist could confirm a role for LdT in enhancing the incidence of the focal axonal lesions. Since the same lesions were also seen in control animals, it was not possible to attribute causality to LdT. Peripheral neuropathy was also absent from other species and pharmacology studies did not show a signal for peripheral neuropathy (LdT is not able to become a substrate for DNA polymerase α, β and γ). The no observed adverse effect level or dose (NOAEL) in monkeys was determined to be 1000 mg/kg/day (6-fold over human AUC).
- While CK elevations and myopathy have been seen among LdT subjects in clinical trials, the histopathologic examination conducted in repeat dose toxicity studies did not show lesions associated with skeletal or heart muscle from monkeys, mice, or rats. CK levels were not included in the preclinical toxicity testing program, with the exception of CK values monitoring in a 14-day intravenous study in monkeys. There were no significant findings related to CK levels in this study.
- LdT may have been related to the death of some rats in the long-term oral gavage carcinogenicity study (104 weeks), due to a slightly higher incidence of nephropathy-related deaths in the 1000 and 2000 mg/kg/day male rates and the 2000 mg/kg/day female rats compared to concurrent male and female controls. Chronic progressive nephropathy (CPN) occurs spontaneously and often in older Sprague-Dawley rats, but the shortened lifetime in the highest dose group (2000 mg/kg/day), which exceeded the lifetime of rats in the control and other dosing groups raises questions regarding the role of LdT in the development of this renal toxicity. Dosing was stopped after 85 weeks of drug administration for the 2000 mg/kg/day dose group because of the high mortality rate in this group. While CPN should be considered a specific disease in rats and not just a manifestation of the aging process, its pathogenesis is not known. Also, CPN does not have a counterpart among the human diseases associated with chronic renal failure.[14] The clinical implications of this LdT-associated increase in the incidence of nephropathy-related deaths among Sprague-Dawley rats remain unclear. The no observed adverse effect level or dose (NOAEL) in rats was 500 mg/kg/day (4-fold over human AUC). There was no renal toxicity in studies conducted in monkeys, mice, rabbits, or woodchucks.

[14] Hard GC and Khan KN "A contemporary overview of chronic progressive nephropathy in the laboratory rat, and its significance for human risk assessment." Toxicologic Pathology 2004; 32:171-180.

MO Comments
Nucleoside analogues have been associated with specific target organ toxicities including neuropathy, myopathy, and nephropathy. The spinal cord and sciatic axonopathy described above do not appear to be true preclinical concerns, given the similar axonopathic findings in control animals. Also, the outcomes of a search of the clinical database for sensory/neuropathic and nephropathic adverse events are described below in Section 7.1.4, Other Search Strategies.

In a battery of four assays with and without metabolic activation, LdT was not shown to be genotoxic. In addition to the absence of mutagenic and/or clastogenic potential in those assays, there was no evidence of a carcinogenic potential in either the Sprague-Dawley rat or the rasH2 transgenic mouse. Sprague-Dawley rats developed the tumors expected with aging, with incidence rates, timing of onset and malignancy types that were similar across all dosing groups, including controls. The FDA Animal Pharmacology/Toxicology reviewer agreed with the Applicant's finding that does not appear to be a carcinogen. Many of the deaths were caused by tumors, but no statistically significant or dose related increase in the incidence of tumor and/or tumor type and deaths attributable to any tumor type was observed. In summary, the NOAEL for carcinogenicity was 2000 mg/kg/day with a systemic exposure 14-fold higher than that at the clinical dosage of 600 mg/day.

LdT can cross both the blood-testes and placenta barrier. Fertility and general reproductive and developmental toxicity of LdT were examined in rat and rabbit studies. Rat studies evaluating doses up to 1000 mg/kg/day did not show maternal toxicity, but the fertility rates were lower in rats given 500 and 100 mg/kg/day. In additional fertility studies of male and female rats at LdT doses up to 2000mg/kg/day, there was no reduction in fertility or development of maternal/fetal toxicity. Male and female fertility were not affected at doses as high as 3000 mg/kg (about 14-times human exposure) in rats. In the rabbit development toxicity studies, however, maternal toxicity (lower body weight and mean food consumption) was noted, in contrast with the control rabbits. One doe aborted and three does delivered their fetuses prematurely in the high dose group (1000 mg/kg/day). The study director attributed these pregnancy losses to maternal toxicity, not abnormal fetal development. LdT was not shown to be a developmental toxin in either rabbits or rats at doses up to 1000 mg/kg/day. Doses up to 1000 mg/kg/day did not alter behaior or postnatal development, growth, sexual maturity or fertility. LdT is secreted into rat milk and exposure to this drug *in utero* or in milk did not affect pup delivery or neonatal development in rats. As noted by Dr. Yuen, the No-adverse-effect level (NOAEL) for reproductive toxicity is 1000 mg/kg/day, providing 6 to 37-fold safety margins as compared to clinical dose of 600 mg/day.

Additionally, LdT did not demonstrate much *in vitro* toxicity in cultured human hepatoma cells, peripheral blood mononuclear cells, bone marrow progenitor cells and several other cell lines of human and other mammalian origin. As discussed in Section 6.1.5, Clinical Microbiology, *in vitro* mitochondrial toxicity was not observed. LdT was not observed to affect local tolerance assessed by contact allergic potential using the murine local lymph node assay.

LdT safety was evaluated in the preclinical animal efficacy studies with the woodchuck hepatitis virus (WHV)[15] and found to have a low incidence and severity of toxicity. The doses used in these efficacy studies, however, were lower than other preclinical toxicity studies and expected to achieve a significantly lower level of systemic exposure.

[15] The principal properties of the DNA polymerases of the woodchuck hepatitis virus and hepatitis B virus are similar.

In the 4-week study of woodchucks chronically infected with woodchuck hepatitis virus (WHV), the animals were treated orally with once daily doses of 0.01, 0.1, 1 and 10 mg/kg LdT (3 animals/group). Controls received LAM 10mg/kg/d or vehicle alone. Viral load decreased in a dose-dependent fashion in LdT-treated animals, with woodchucks in the 10mg/kg/day group achieving undetectable virus (dot-blot assay) following day 14 and an almost 8 log drop from baseline by quantitative PCR assay. In contrast, the LAM-treated animals achieved a < 1 log decrease in viral load through day 28. The Applicant reports that drug-related toxicity was not observed during the 4-week study or the 8-week follow-up period.

In the 12-week study of chronically WHV-infected woodchucks, they were treated orally with once daily doses of 1 mg/kg LdT (4 animals/ group). The study was also exploring the antiviral effect of LdT alone and in combination with valtorcitabine (val-LdC), another Idenix investigational drug. Woodchucks in the LdT group achieved a 7-log decrease in viral load by the end of treatment. By 6 weeks post-treatment, viral load returned to levels close to baseline. WHsAg levels also declined during treatment, but they also returned toward baseline post-treatment. The LdC and LdT combination resulted in a greater than expected antiviral response. The Applicant reports that there was no drug-related toxicity observed during the 12-week study or the 12-week follow-up period.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data generated by the Applicant during clinical trials of LdT were the sources of data for this review. The primary source of clinical safety and efficacy data was derived from Study NV-02B-007, the pivotal, randomized, double blind, LAM-controlled, Phase 3 clinical study of LdT in HBeAg-positive and HBeAg-negative subjects with chronic HBV and compensated liver disease. Additionally, data generated during the Phase 2b dose-finding study, NV-02B-003, and its follow-on study, NV-02B-010, were also reviewed, primarily for safety.

Additional safety data, albeit limited, were also available at the time of this NDA submission for several Phase 1 and Phase 2 studies. Data from Phase 1 and Phase 2 studies are mentioned as supportive evidence of the Phase 3 safety assessment. All clinical studies submitted with this NDA are listed below in Section 4.2, Table of Clinical Studies.

Scientific literature and the labels of select lipid-lowering agents were also reviewed for information on toxic myopathies and CK elevations. The Executive Summary, provided by the Applicant, of their Telbivudine Creatine Phosphokinase Roundtable Discussion (held on January 26, 2006) was reviewed. Additionally, archived Medical Officer reviews of LdT-related submissions, and minutes from the pre-NDA Meeting, End-of-Phase 2 Meeting, and other pivotal communications with the Applicant were reviewed. Please refer to Section 2.5 for specific details on presumbission regulatory activities.

4.2 Tables of Clinical Studies

The LdT clinical development program includes 24 clinical trials, all of which are summarized

below in Table 4.2A. Subjects were given either LdT alone, at various doses once daily, or in combination with other anti-HBV drugs (See drug interaction studies listed below). Among the 24 clinical trials, 9 were conducted in subjects with chronic hepatitis B infection. The clinical studies reviewed in detail for this NDA are the pivotal trial, NV-02B-007 and the key supportive studies, NV-02B-003 and its follow-on study, NV-02B-010. The Applicant's reports of the ongoing Phase 3 and early Phase 1/2a studies were also reviewed for safety. The pharmacokinetic data from the clinical pharmacology studies (Phase 1 and 2) were reviewed in detail by the Clinical Pharmacology/ Biopharmaceutics Reviewer, Dr. Jennifer Zheng.

Table 4.2A Clinical Trials in the LdT Clinical Development Program

Study	Study Type	Country or Continent	Design	Study Population	Dose and Duration	Total No. of Subjects	Primary Efficacy Endpoint and/or Status
Phase 3 or 3b							
NV-02B-007 (GLOBE Trial)	Pivotal safety and efficacy	Asia, North America, Europe Oceania,	Randomized, DB, LAM control;	HBeAg +/- CHB, nucleoside-naïve; compensated liver dz	LdT 600mg qd X 104 weeks	LdT-680 LAM-687	Serum HBV DNA < $5\log_{10}$ copies/mL *with* ALT normalization or HBeAg loss[16] Ongoing (52 wk data submitted w/ NDA)
NV-02B-011	LT safety and efficacy	Asia, North America, Europe, Oceania	Randomized, DB, LAM control;	HBeAg+/- CHB; decomp liver dz	LdT 600mg qd x 104 weeks	90	HBV DNA < 4 $\log_{10}$ cop/mL & normal ALT level *and* improvement/ stabilization in CTP score -52 wks. Ongoing
NV-02B-015	LT safety and efficacy	China	Randomized, DB, LAM control;	HBeAg +/- CHB; nucleoside-naïve; compensated liver dz	LdT 600mg qd x 104 weeks	332	Ongoing (52 wk safety data submitted with 120D Safety Update)
NV-02B-018	LT safety and efficacy; Drug Comparison	Asia, France, North America, Austrailia	Randomized, Open label	HBeAg +/- CHB; nucleoside-naïve; compensated liver dz	LdT 600mg vs ADV 10mg X 52 weeks	136	Ongoing
NV-02B-019	LT safety and efficacy of switching LAM	Israel	Randomized, switching LAM to LdT v. Continued LAM	HBeAg +/ CHB; compensated liver dz	LAM 100mg v. LdT 600mg x 52 weeks	177	Ongoing
NV-02B-022	LT safety and efficacy	Asia, North America, Europe Oceania,	Open-Label, Non-comparative, LdT rollover from Idenix-sponsored LdT studies	HBeAg+/- CHB	LdT 600 mg	128	Ongoing

[16] The key secondary endpoints for NV-02B-007 were histologic response defined as a greater than 2-point reduction in the Knodell necroinflammatory score with no worsening in the fibrosis component score. The study was adequately powered for this key secondary endpoint of histologic response assessed at week 52.

Study	Study Type	Country or Continent	Design	Study Population	Dose and Duration	Total No. of Subjects	Primary Efficacy Endpoint and/or Status
Phase 2b							
NV-02B-003	LT safety and efficacy	Canada, US, Hong Kong, Singapore, France, Puerto Rico	randomized, DB, active and placebo control	HBeAg +; compensated liver dz	LdT 400mg vs. 600mg vs. LAM 100mg vs. Both x 52weeks	107 (approximately 20/group)	Weeks 1 to 12 log_{10} HBV DNA AUC minus baseline Completed
NV-02B-010 (follow-on study of NV-02B-003)	LT safety and efficacy	Canada, US, Hong Kong, Singapore, France, Puerto Rico	randomized, DB, active control	HBeAg + CHB; compensated liver dz	LdT 600mg vs. LAM 100mg vs. Both x 52weeks	90	Ongoing, interim
Phase 2a, Multiple dose Phase 1 PK studies (excluding BA/BE),							
NV-02B-001	PK, safety and efficacy	Hong Kong, Singapore	Randomized, DB, placebo-controlled, dose escalation	HBeAg+ CHB	LdT:25, 50, 100, 200,400, 800 mg/d x 4 weeks	43	HBV DNA reduction response to treatment at Week 4 Completed
NV-02B-024	PK/PD/ cardiac safety (thorough QT study)	US	Randomized, Partially SB, placebo and active (moxifloxacin) Controlled, 4-pd crossover	Healthy subjects	LdT 600mg v. LdT 1800 mg v. moxiflox x 14 days	62 (31 male/31 female)	QT interval, PK and PD
NV-02B-002	PK; drug interaction with LAM; safety & tolerability	US	Open-Label, Multi-dose	Healthy Subjects	LdT 200mg x 14 days; LAM 100mg	16 (8/group)	PK Complete
NV-02B-012	PK; drug interaction with peg-IFN; safety & tolerability	US	Open-Label, Multi-Dose	Healthy Subjects	LdT 600mg v. peg-IFN x 14 days	18	PK Complete
NV-02B-013	PK; drug interaction with ADV; safety & tolerability	US	Open-Label, Randomized, parallel group, multi-Dose	Healthy Subjects	LdT 600mg v. ADV x 7-15 days	16 (8/group)	PK Complete
NV-02B-023	PK; drug interaction with cyclosporine; safety & tolerability	US	Open-Label, Multi-Dose	Healthy Male Subjects	LdT 600mg v. cyclosporine x 5-9 days	20 (10/group)	PK Complete
NV-02C-003	PK; drug interaction with LdC; safety & tolerability	US	Open-Label, Randomized, Crossover	Healthy Subjects	LdT 600mg on Days 1, 8, & 15	12 (2/group)	PK Complete, but only synopsis available at NDA submission
NV-02B-016	PK in Chinese subjects	China	Open-Label, Randomized, Dose ranging	Healthy Male Subjects	LdT: 200,400, 600, 800 mg/d x 9 days	42 (12/group-600mg and 10/group other doses)	PK Complete
NV-02B-004	PK, Safety & Tolerability by gender	US	Open-Label, Multi-dose, Fasting PK	Healthy Subjects	LdT 800mg x 7 days	12 (6 per gender)	PK, Safety Complete
Single Dose Phase 1, PK (excluding BA/BE)							
NV-02B-006	PK in renally impaired; safety &	US	Open-Label, Single Dose	Renal Impaired/ Healthy Subj	LdT 200mg; LdT 400mg; LdT 600mg	36 (8/group normal, mild,	Complete

Study	Study Type	Country or Continent	Design	Study Population	Dose and Duration	Total No. of Subjects	Primary Efficacy Endpoint and/or Status
	tolerability				x 1day	moderate) (6/group severe ESRD)	
NV-02B-005	PK in hepatically impaired; safety & tolerability	US	Open-Label, Single Dose	Hepatically Impaired/ Healthy Subj	LdT 600mg x 1 day	24 (6/group)	Complete
NV-02B-009	PK following radiolabeled LdT; Safety	US	Open-Label, single dose ^{14}C-ADME	Healthy Male Subjects	LdT: 600 mg; 100 µCi; solution Form; x 1 day	6	Complete
D35001007	Safety and PK in Japanese Male Subjects	Japan	DB, Randomized, placebo-controlled	Healthy Japanese Subjects	LdT: 200,400, 600, 800 mg/d x 1 day	32 (6 active; 2 placebo/group)	Complete
Phase 1 Bioavailability and Bioequivalence							
NV-02B-008	Bioavailability; safety and efficacy		Open-Label, single dose, crossover	Healthy Subjects	LdT 600mg X 2 days	24 (12/group)	Complete
NV-02B-014	Bioequivalence of 4 oral formulations		Open-Label, Randomized, 4-way crossover	Healthy Subjects	LdT 600mg (3 tabs of 200 mg LdT vs. 1 tab of 600 mg LdT vs. 30 mL x 20 mg/mL of LdT) x 4 days	12 (3/group)	Complete
NV-02B-025	Bioequivalence of clinical and to-be-marketed formulation; Safety, Pivotal		Open-Label, Randomized, 3-way crossover	Healthy Subjects	LdT 600mg (3 tabs of 200 mg LdT vs. 1 tab of 600 mg LdT vs. 30 mL x 20 mg/mL of LdT) x 3 days	24 (8/group)	Complete

Source: Adapted from Section 5.2 Tabular Listing of All Clinical Studies (Telbivudine) in NDA 22-011

4.3 Review Strategy

The Clinical Review of NDA 22-011 was conducted by Dr. Charlene Brown, a Medical Officer in the Division of Antiviral Products. In addition to the Clinical Review, Dr. Fraser Smith, Mathematical Statistical Reviewer, conducted primary and secondary efficacy endpoint analyses and selected subgroup analyses for the pivotal trial, NV-02B-007. Review of the efficacy and safety data was conducted for the pivotal study, NV-02B-007. Studies NV-02B-003 and NV-02B-010 were evaluated separately since they were small, Phase 2b studies in which only a small subset (22 subjects) of subjects received the to-be-marketed dose of LdT, 600mg. The Phase 1 and Phase 2 Studies were reviewed for dose-response by the Clinical Pharmacology Reviewer, Dr. Jennifer Zheng. The animal toxicity and carcinogenicity sutides were evaluated by Dr. Ita Yuen, the Pharmacology/Toxicology Reviewer and the Chemistry, Manufacturing and Control (CMC) issues were reviewed by Dr. Ko-Yu Lo. Blinded data from ongoing studies, including rollover studies, were reviewed only for death and specific serious adverse event (SAE) information, but were not

otherwise reviewed in detail for this NDA. This review integrates and summarizes the multi-disciplinary findings of the other reviewers with the findings of the primary Medical Reviewer.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) performed on-site investigations on a subset of NV-02B-007 study sites. Because of the large number of sites and investigators and the relatively small number of subjects enrolled in the clinical trials at each site, a small proportion of sites, investigators, and enrolled subjects were audited. The study sites were reviewed for study size and recent DSI inspections. A list of sites and principal investigators who had contributed the largest numbers of subjects to the pivotal clinical trials and had not also had a recent, satisfactory DSI inspection was provided to DSI. Most sites for the NV-02B-007 were not based in the United States. Consequently, four foreign sites were selected for data audit:

- Site# 008 (Yun-Fan Liaw, M.D.- Taiwan, Republic of China)
- Site# 50 (Satawat Thongsawat, M.D.-Chaing Mai, Thailand)
- Site# 041(William Seivert, M.D.- Clayton , Australia)
- Site# 057 (Edward Gane, M.D.- Auckland, New Zealand

DSI inspections did not reveal any findings that might compromise the integrity of the data submitted with the NDA submission. For a more detailed discussion of the DSI audit, please refer to the Clinical Inspection Summary, by Dr. Antoine El-Hage, Regulatory Pharmacologist. The Clinical Inspection Summary is part of the NDA Action Package.

4.5 Compliance with Good Clinical Practices

Per the Applicant, all clinical studies were conducted in accordance with International Committee on Harmonization (ICH) Good Clinical Practice Standards, including the archiving of essential documents. All clinical trial subjects provided informed consent in writing prior to the initiation of study procedures.

The Applicant also conducted 19 routine investigator site audits throughout the implementation of the NV-02B-007 clinical trial. These audits enabled Idenix to investigate whether or not these study centers were in compliance with the protocol, local and FDA regulations and guidelines, as well as ICH Good Clinical Practice guidelines.

There were a total of 62 subjects who were inadvertently randomized to the wrong strata in the Interactive Voice Response Services (IVRS)[17] based on subjects' central laboratory results at the Screening visit. Among them 33 were for ALT results only, 28 were for HBeAg results only and 1 subject was for both ALT and HBeAg results.

As shown below in Table 4.5.1, the number of protocol violations, including protocol exemptions, was relatively similar between treatment groups. This similarity was maintained when protocol

[17] The IVRS, in addition to its role in managing clinical trial material inventory, was used to randomly assign subjects to treatment groups in the LdT Phase 3 trial, NV-02B-007.

violations were examined by HBeAg status.

Table 4.5.1: NV-02B-007: Protocol Exemptions and Key Study Deviations, Up to Week 52

	Lamivudine	Telbivudine	Total
Overall patients enrolled, N	**687**	**680**	**1367**
Protocol deviation for enrollment, n (%)	43 (6.3)	38 (5.6)	81 (5.9)
Exemption granted by Sponsor, n (%)	36 (5.2)	29 (4.3)	65 (4.8)
Noncompliant with treatment up to Week 52*	5 (0.7)	5 (0.7)	10 (0.7)
Took prohibited medication up to Week 52§, n (%)	4 (0.6)	0	4 (0.3)
HBeAg-positive patients enrolled, N	**455**	**445**	**900**
Protocol deviation for enrollment, n (%)	27 (5.9)	21 (4.7)	48 (5.3)
Exemption granted by Sponsor, n (%)	22 (4.8)	15 (3.4)	37 (4.1)
Noncompliant with treatment up to Week 52*	3 (0.7)	4 (0.9)	7 (0.8)
Took prohibited medication up to Week 52§, n (%)	2 (0.4)	0	2 (0.2)
HBeAg-negative patients enrolled, N	**232**	**235**	**467**
Protocol deviation for enrollment, n (%)	16 (6.9)	17 (7.2)	33 (7.1)
Exemption granted by Sponsor, n (%)	14 (6.0)	14 (6.0)	28 (6.0)
Noncompliant with treatment up to Week 52*	2 (0.9)	1 (0.4)	3 (0.6)
Took prohibited medication up to Week 52§, n (%)	2 (0.9)	0	2 (0.4)

*Patients excluded from the EE population.
§Includes only medications that disqualify subsequent data from the EE analysis.
Source: Table 10-4, NV-02B-007 Full Clinical Study Report

MO Comments:
The number of protocol violations was not unusually high and the pivotal trial appears to have been conducted in accordance with acceptable ethical standards.

4.6 Financial Disclosures

The Applicant included in the NDA submission a list of investigators and subinvestigators with no financial interests to disclose per 21 CFR Part 54. FDA Form 3455 was filed for 1 investigators participating in the LdT pivotal trial as described below.

Dr. Nikolai Naomov received financial payments for the conduct of *in vitro* T-cell substudies to evaluate the potential impact of LdT on T-cell function in subjects with HBV infection. Dr. Naomov, an Investigator in the NV-02B-007 trial, was not unblinded to individual subject treatment assignments.

MO Comments
Participation of Dr. Naomov in the pivotal LdT trial is very unlikely to have had any effect on the integrity of the study or the efficacy and/or safety conclusions drawn based on the data.

5. CLINICAL PHARMACOLOGY

Please refer to Dr. Jennifer Zheng's Clinical Pharmacology and Biopharmaceutics review for a detailed analysis of the pharmacokinetics (PK), pharmacodynamics (PD) and exposure-response relationship of LdT. A summary of the important PK, PD and exposure-response issues raised in Dr. Zheng's review are presented below.

5.1 Pharmacokinetics

In the NDA submission, the Applicant supplied information describing the PK profile of LdT, including metabolism, absorption, distribution, and excretion. Table 5.1A and 5.1B provide summaries of single dose PK parameters after the proposed therapeutic dose (600mg).

Table 5.1.A: Summary of PK parameters of LdT in Healthy Subjects[a]

Mean(SD)	C_{max}(ng/mL)	**Tmax***(h)	C_{trough} (ng/mL)	AUC_0-∞/AUC_{ss} (ng/mL-h)	$T_{1/2}$ (h)
600 mg single dose	3704 (1219)	2.0 (0.5 -3.0)	NA	26441(8938)	39.4 (12.1)
600 mg steady-state[b]	3590 (1247)	2.0 (1.0 -4.0)	252.7 (74.0)	26124 (7196)	48.8 (10.5)

*median (range)
Source: FDA Clinical Pharmacology Review, Dr. Jennifer Zheng
[a] Table based on Study NV-02B-016 (n = 42).
[b] Steady-state LdT PK parameters collected 13 days after administration of 600 mg LdT once daily in healthy subjects.

LdT PK was not studied in subjects with chronic hepatitis B at the to-be-marketed dose of 600mg. Based only on the population PK analysis in healthy subjects and one Phase 1/2a study in subjects with chronic HBV, the LdT PK parameters in subjects with chronic HBV were estimated. The predicted steady-state concentration-time profiles for healthy volunteers and subjects with chronic HBV and Creatinine Clearance ≥ 50 mL/min receiving LdT 600 mg/day were estimated by population PK analysis.

Table 5.1.B: Summary of Predicted PK parameters of LdT in Hepatitis B patients

	C_{max}(ng/mL)	**Tmax***(h)	AUC_{ss} (ng/mL·h)	$T_{1/2}$ (h)
600 mg single dose	2683 (695)	2.1 (0.8 -4.8)	NA	NA
600 mg steady-state	3251 (866)	2.1 (0.8 -4.1)	31679(15461)	51.4 (18.7)

*median (range)
Source: FDA Clinical Pharmacology Review, Dr. Jennifer Zheng

MO Comments
Given the efficacy and safety data for the 600 mg once daily dose in chronic HBV subjects through the NV-02B-007 trial and Population PK analysis, it is unlikely that there would be a significant difference between PK parameters in individuals with chronic HBV and healthy subjects.

LdT has a long plasma terminal elimination half life (~40 hours). Steady state, however, was achieved after 5 to 11 days of once-daily LdT administration with approximately 1.5-fold accumulation. Thus LdT has an effective half-life for acummulation of approximately 15 hours. LdT clearance did not change with chronic dosing.

Food effect studies show that LdT absorption and exposure were unaffected when a single 600 mg dose was administered with a high-fat (54.6 g), a high-calorie (950 kcal) meal. It will be recommended that LdT may be dosed with or without food.

In addition, LdT demonstrated low plasma protein binding (3.3%). Given that the estimated apparent volume of distribution is in excess of total body water, LdT appears to be widely distributed after oral administration. After a radioactive oral 600mg dose of LdT, 91.6% of total dose was recovered in the urine (41.9%) and feces (49.6%) within 168 hours of dosing. LdT was excreted primarily in urine by passive diffusion, resulting in a low likelihood for interaction between LdT and other renally-excreted drugs.

LdT was not metabolized in humans. In addition, LdT was not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system based on an *in vitro* study. While an animal study showed that LdT is not an inducer of CYP enzymes, it remains unknown whether or not LdT is an inducer of CYP enzymes in huamns.[18] It is not known if LdT is a substrate for the transporter P-glycoprotein because a positive control (digoxin) was not included in the study. Also, the potential for LdT to inhibit P-glycoprotein was not evaluated.

MO Comments
For improved understanding of potential drug-drug interactions, the Applicant will be asked to evaluate CYP induction potential for LdT using in vitro or in vivo studies. They will also be asked to evaluate if telbivudine is a Pgp substrate or inhibitor. See Dr. Zheng's Clinical Pharmacology Review for additional details.

Subjects with hepatic impairment do not require dose adjustment for LdT, given the excretion pathways. Dose adjustment, however, is necessary for patients with moderate to severe renal impairment (CRCL < 50 mL/min), including patients with end-stage renal disease (ESRD) on hemodialysis. Subjects on continuous ambulatory peritoneal dialysis (CAPD) were not evaluated. Following a single 200 mg dose of LdT, a 4-hour hemodialysis session removed approximately 23% of the LdT dose within 2 hours of the dose. Based on simulations performed to assess the effects of varying degrees of renal impairment on LdT PK, the following dose interval adjustments were proposed by the Applicant (see Table 5.1.C).

Table 5.1.C Dose Interval Adjustment of LdT in Patients with Renal Impairment

Creatinine clearance (mL/min)	**Dose of LdT**
≥ 50	600 mg once daily
30 – 49	600 mg once every 48 hours
< 30 (not requiring dialysis)	600 mg once every 72 hours
ESRD	600 mg once every 96 hours

Source: Table 2.3.1b, FDA Clinical Pharmacology Review, Dr. Jennifer Zheng

[18] No *in vitro* studies in human hepatocytes or *in vivo* human studies has been conducted to show telbivudine is not an inducer of CYP enzymes.

The Applicant's proposed change in dosing interval results in slightly higher Cmax estimates as renal function decreases, although the increased C_{max} is not higher than the value obtained after 800mg once daily administration, which was the highest dose used in the Phase 1/2a dose-finding trial (NV-02B-001). Limited duration changes in dosing interval results in comparable exposures at steady-state although Cmax estimates are slightly increased as renal function is decreased. Limited (4 wk) data in this trial showed antiviral efficacy without significant adverse events among subjects on the 800mg dose.

MO Comments
The limited duration (4 wks) and study population size (n=43) of NV-02B-001 provides a very limited safety database for the safety profile associated with the Cmax associated with exposures in patients with severe renal impairment (Cmax of the 800mg dose.) It is not known if longer-term dosing at 800mg may result in new toxicities or increased rates of toxicities relative to those seen with the 600mg dose in the NV-02B-007 trial. It is unknown whether or not there is a dose-relationship between adverse events and LdT dose. Consequently, it is not known whether or not these subjects may be at a greater increased risk of adverse events, including the adverse event of myopathy relative to the subjects receiving the 600mg dose.

Also, due to the limited toxicity database and the increased PK fluctuation seen with dose interval changes for renally impaired subjects, dose reduction is preferred over dose interval adjustment. The FDA has communicated this preference to the Applicant and the Applicant [redacted] *. Given the overall acceptable safety profile associated with LdT 600mg, the dose adjustment proposed by the sponsor is acceptable as an interim solution.*

There was no alteration of LdT PK with LAM, ADV, cyclosporine and pegylated interferon-alfa 2a in drug-drug interaction studies. In addition, LdT does not alter the PK of LAM, adefovir dipivoxil, or cyclosporine. It was not possible to draw definitive conclusions regarding the effects of LdT on the PK of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.

The pharmacokinetics of LdT are not significantly affected by gender, race and hepatic impairment, but is affected by renal impairment. In the population PK analysis, LdT steady-state PK were predicted for Caucasian, African American, and Asian subjects, revealing no significant differences between the subjects in these categories. Dose adjustment based on race, age, or gender is not recommended. In addition, based on the PK results for heavy-weight subjects in NV-02B-001, clinically significant differences in efficacy based on weight were not expected. Dose adjustment based on weight is not recommended.

5.2 Pharmacodynamics

The Clinical Pharmacology Reviewer assessed dose proportionality by a power model, finding that the area under the concentration-time curve (AUC) at steady state increase was less than dose-proportional subsequent to multiple once daily doses or a single dose ranging from 200 mg to 800 mg. These findings do not support the Applicant's claim that LdT PK is dose proportional over the range of 25mg to 1800mg.

There was no uniform, dose-related pattern seen in the occurrence of specific adverse events among subjects in the Phase 1-2 LdT clinical development program. With the exception of 2 subjects (2/16) with an adverse event of pallor in the LdT and LAM drug interaction study (NV-02B-002,) and 3/24 subjects with clinically significant low platelet counts in single-dose hepatic impairment study (NV-02B-005), the common adverse event pattern among LdT subjects in the Phase 1-2 studies was generally similar to the pattern seen among LdT subjects in the pivotal trial. While there were subjects with chronic HBV in the Phase 1-2 LdT that received up to 800mg of LdT, only healthy subjects received 1800 mg of LdT. Also, as discussed below in Section 7, the Integrated Review of Safety, CK elevations were more common among subjects on LdT than LAM in the pivotal trial. Most studies in the Phase 1-2 clinical development program did not measure CK elevations, however, a higher rate of CK elevations among LdT subjects was noted in the Phase 2b dose finding study, NV-02B-003. While there were cases of myopathy with muscle weakness (requiring study drug discontinuation) seen among LdT subjects in the pivotal trials (3/680), there were no diagnosed cases of myopathy or myositis among LdT subjects in the Phase 1-2 LdT development program. There were also no deaths among LdT subjects in the Phase 1-2 LdT development program.

MO Comments
Conclusions cannot be drawn regarding the safety of 1800mg LdT in subjects with chronic HBV since only healthy subjects received this higher dose. The Applicant's original proposed label was modified to reflect this.

A thorough QT study (NV-02B-024) was conducted in sixty-two subjects (31 male/ 31 female) who met criteria for a negative, thorough QT study. The results showed no effect on QT_cf interval after LdT at the to-be-marketed dose, 600 mg once daily, or the supra-therapeutic dose (1800 mg/day) in a thorough QT study. Moxifloxacin, however, was positive (within the range of reported values in the literature for QT_c prolongation.) There was no increase in QT_cf with increasing plasma LdT concentration.

The QT study was a phase 1, randomized, partially single-blinded, placebo and active (moxifloxacin) controlled, four-period crossover study. All subjects were randomized to one of four treatment sequences of two telbivudine doses, moxifloxacin, and placebo, with a two-week washout period between treatments. Subjects received both LdT doses (600 and 1800 mg) and placebo for 7 days. Moxifloxacin (400 mg) was administered only on Day 7.

Fridericia's corrected QT (QT_c F) was constant with increased heart rates, and was deemed to be the best measurement for QT. On Day 7, the 15 time-matched placebo-adjusted changes from baseline demonstrated that neither dose of LdT was greater than the threshold of 10 msec for the upper limit of the 95% confidence interval (CI) at any timepoint. These changes appeared relatively consistent between dose groups. The LdT 600mg dose group and the 1800 mg dose group both showed a similar profile over time for Day 7, supporting the finding that there was not an effect of either of these LdT doses on the QT_c F interval.

Among subjects in the thorough QT study, there were 9 study drug (SD) discontinuations (only 1 due to an AE), one SAE, unrelated to SD, and common AEs similar to the common AE profile seen in other studies of LdT.

Please see Section 7.1.9.1, Electrocardiograms, for additional discussion of Study NV-02B-024.

5.3 Exposure-Response Relationships

As noted above in Section 5.2, Pharmacodynamics, the dose-response data from NV-02B-001 predicted that the optimal antiviral efficacy for LdT was in the 400mg to 800mg dose range. The 400 mg/d and 800 mg/d dose groups experienced median reductions in HBV DNA of 3.63 log10 and 3.75 log10 copies/mL, respectively at the end of four weeks of treatment. Also, the data from the Phase 2b dose-finding trial NV-02B-003, showed maximal antiviral efficacy at the 400mg and 600 mg once daily dose. Ultimately the 600mg dose was selected based on both the Emax model, which predicted approximately a 0.2 $\log_{10}$ (~40%) greater antiviral effect over the 400 mg/d dose and only 0.1 $\log_{10}$ less than the 800 mg dose, while allowing a convenient tablet size, and possibly reducing the likelihood of safety concerns that might occur at a higher dose.

On June 17, 2002, at the End-of-Phase 2 Meeting, both the Division of Antiviral Products and the Applicant agreed upon the use of the 600mg LdT dose in the Phase 3 registrational trials.

6. INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

Data from the pivotal, Phase 3 study, NV-02B-007, were used in the primary efficacy review to support the proposed indication. This study compared the treatment effects of LdT versus LAM on the primary efficacy endpoint, a new composite endpoint called Therapeutic Response, defined as:

- Loss of detectable serum HBeAg or ALT normalization
  and
- Serum HBV DNA < 10^5 copies/ml by the COBAS Amplicor™ PCR assay.

The study also evaluated the treatment effects of LdT compared to LAM on a variety of secondary histologic, virologic, serologic, biochemical, and composite efficacy endpoints.
Subjects were to be pre-stratified by HBeAg status (positive or negative) and ALT (greater than or less than 2.5 times the ULN) at screening. The principal treatment comparisons for the primary efficacy endpoint in this NDA were based on the data available after one year of treatment.

In this study, subjects were not allowed to have received interferon (IFN) or other immunomodulatory treatment for HBV infection in the 12 months prior to Screening. Subjects were also excluded if they had received LAM or an investigational nucleoside or nucleotide analogue for treatment of Hepatitis B, at any time. Please refer to Section 6.1.3 for more details on the NV-02B-007 study design and inclusion/exclusion criteria.

Additionally, results generated during the Phase 2b dose-finding study, NV-02B-003, and its follow-on study, NV-02B-010, were reviewed briefly for efficacy. The primary efficacy objective of NV-02B-003 was to assess whether or not there was a difference in antiviral efficacy between LdT 400mg once daily alone, LdT 400mg once daily in combination with LAM, LdT 600mg once daily alone and LdT 600mg once daily in combination with LAM versus LAM alone. The outcomes of this study are discussed above in Section 5.3 Exposure-Response Relationships.

The NV-02B-003 follow-on study, NV-02B-010 was designed to provide longer-term efficacy and safety data for LdT alone and in combination with LAM. The study was underpowered, however, for its intended efficacy assessment which was to determine whether the treatment differences observed after 52 weeks in NV-02B-003 remained after longer term treatment.

6.1.2 General Discussion of Endpoints

Historically, the Division of Antiviral Products (DAVP) has required histologic endpoints in the analysis of efficacy for drugs used in the treatment of chronic HBV. Improvement in liver histology has been considered a surrogate for the development of HBV-related complications (cirrhosis, liver transplantation, hepatocellular carcinoma) and death, the true endpoints.

The Applicant initially proposed a novel, composite, primary efficacy endpoint, Therapeutic Response, for its registrational trial, but the Division preferred to use histologic response as the primary efficacy endpoint, initially due to the lack of public input and data supporting the use of a non-histologic primary endpoint.

In August 2002, prior to the September 2002 approval of ADV, the DAVP convened an issue-oriented Advisory Committee to discuss the design of clinical trials for treatment of HBVand the appropriate efficacy endpoints to be considered for drug approval. At that time, extensive statistical evaluation of data generated during the LAM and ADV clinical trials was presented. These data showed poor capacity of virologic (HBV DNA levels) and biochemical (ALT levels) endpoints to predict improvement in liver histology after 48 weeks of treatment. The lack of correlation was interpreted by some on the Advisory Committee to suggest that virologic and biochemical measures might not correlate well with clinical outcome, but it was also noted that it is possible that the histology inflammatory score does not actually correlate with clinical outcomes and that the virologic and biochemical markers do correlate with clinical outcome. The limitations of liver biopsy were identified including: risks of the procedure, subjects' hesitation to undergo the procedure, difficulty in obtaining an adequate and representative sample of liver tissue, and limitations on the number of time-points at which samples can be obtained. The possible use of a composite efficacy endpoint as a primary efficacy endpoint in future trials was also discussed at length during the meeting. Some of the Advisory Committee members favored a composite endpoint (e.g. combination of virologic, biochemical and or serologic endpoints), while others advocated for maintaining the primacy of a primary histologic endpoint. The Committee acknowledged that neither a histologic endpoint nor a composite endpoint is a perfect measure of efficacy and that neither is proven to correlate with clinical outcome. There appeared to be consensus, however, among Committee members that the population being treated and the goals of

therapy should, at least partially, influence the selection of the primary endpoint. The Agency was encouraged to remain cognizant of this and flexible in its selection of endpoints. [19]

Subsequent to public and expert input garnered through the August 2002 HBV Advisory Committee meeting and continued communications with Idenix, the Division eventually accepted histologic response as an important secondary efficacy endpoint in written comments faxed to the Applicant on October 29, 2002. The Division noted that as long as paired histology specimens would be obtained from an adequate number of subjects, it was less important whether or not histology is a primary or secondary endpoint. In a teleconference between the Division and the Applicant the next day, both parties agreed that histology could be acceptable as an extremely important secondary efficacy endpoint, concurrent with an appropriate plan to obtain paired biopsy specimens from an adequate number of subjects (which were representative of the study demographics.)

Consequently, a novel, composite, primary efficacy endpoint was selected for the LdT Phase 3 trial, NV-02B-007, termed Therapeutic Response (TR). TR was defined as attainment of serum HBV DNA < 5 log10 copies/mL linked with either HBeAg loss or ALT normalization. As noted in the NV-02B-007 protocol, the composite Therapeutic Response endpoint is conceptually related to the composite "Virologic Response" endpoint used in early interferon trials in HBeAg-positive subjects. Also, a composite serologic endpoint comprising HBV DNA suppression and ALT normalization had been used in several large clinical trials involving HBeAg-negative subjects with chronic hepatitis B. The three-component composite endpoint designated as Therapeutic Response was intended to capture the two forms of clinical efficacy intended for hepatitis B subjects, regardless of HBeAg status. It was proposed that subjects who achieved Therapeutic Response would achieve both the degree of HBV DNA suppression (HBV DNA levels <5 log10 copies/mL) recommended in the AASLD and APASL guidelines, and either HBeAg loss or ALT normalization.

In HBeAg-negative subjects, the Therapeutic Response endpoint was driven only by the ALT and HBV DNA components, and this 2-component use of Therapeutic Response was termed Composite Serologic Response (CSR) in the NV-02B-007 protocol. However, for simplicity, in this review, the Therapeutic Response terminology was used to describe primary endpoint results for both HBeAg-positive and HBeAgnegative subject populations. Therapeutic Response was not considered a treatment discontinuation endpoint for either subpopulation.

MO Comments:
Given the limitations associated with the use of serologic, virologic or histologic endpoints in isolation, this Medical Reviewer supports the use of a composite, non-invasive surrogate endpoint, as the primary efficacy endpoint in the LdT pivotal Phase 3 study. Although, at the time of the phase 3 protocol design, HBV DNA suppression to less than 5log$_{10}$ copies/mL was an appropriate treatment goal, current evidence suggests that reducing viral load as low as possible to < 300 copies/mL may result in a higher rate of histologic improvement compared to a level of 10000 copies/mL or even 1000 copies/ml.[20] Future Phase 3 HBV treatment efficacy studies with a composite endpoint should have a viral load target of <300 copies/mL for maximum therapeutic benefit.

[19]Antiviral Drugs Advisory Committee Meeting Minutes, US Food and Drug Administration, Department of Health and Human Services, August 7, 2002.
[20]Iloeje UH, Yang HI, et al "Serum Hepatitis B Virus DNA Level Predicts the Incidence of Liver Cirrhosis in Persons Chronically Infected with HBV." Abstract from the 2005 Annual Meeting of the European Association for the Study of the Liver.

The principal secondary efficacy endpoint (histologic response) chosen for the LdT Phase 3 study was similar to the primary endpoint used in the development program for ETV and ADV. Improvement in liver histology was defined in all studies as at least a 2-point reduction in the Knodell necroinflammatory score with no worsening in the fibrosis score at Week 52 when compared to the pre-treatment liver biopsy samples. In order to decrease subjectivity in scoring the histology, all biopsies were evaluated by a central pathologist who remained blinded to the subjects' treatment and the temporal order of the biopsies. The pathologist who scored the biopsies for the LdT studies was the same pathologist who evaluated biopsies performed for the ETV and ADV clinical trials, Dr. Zachary Goodman.

Multiple supporting secondary endpoints were considered appropriate for anti-HBV drug assessment. These secondary efficacy endpoints included:

- Knodell Histologic Activity Index (HAI) Score
- Ishak Fibrosis Score
- Change in Ishak Fibrosis Score
- Maintained Therapeutic Response
- Composite Serologic Response (HBeAg-negative only)
- Maintained Composite Serologic Response (HBeAg-negative only)
- Serum HBV DNA
- HBV DNA Non-Detectable (PCR Negative)
- Maintained HBV DNA Non-Detectable
- HBV DNA Suppression
- Maintained HBV DNA Suppression
- HBeAg Loss (HBeAg-positive only)
- Maintained HBeAg Loss (HBeAg-positive only)
- HBeAg seroconversion (HBeAg-positive only)
- Maintained HBeAg seroconversion (HBeAg-positive only)
- Three Component HBeAg seroconversion (HBeAg-positive only)
    - This composite endpoint serves to exclude any clinically significant precore/core mutant HBV and is defined as:
        - HBeAg Seroconversion
        - Serum HBV DNA < 5 log10 copies/mL.
- Virologic Response (HBeAg-positive only)
    - Defined as HBeAg loss and HBV DNA < 5log10 copies/mL
- Maintained Virologic Response (HBeAg-positive only)
- Serum ALT
- ALT Normalization
    - Defined as: ALT within normal limits on 2 successive visit for pt with ALT > 1.0 x ULN at baseline
- Maintained ALT Normalization
- Composite Serologic-Histologic Efficacy
- HBsAg Loss and/or HBsAg Seroconversion
- Met Efficacy Criteria for Treatment Discontinuation, Discontinued or Not
- Treatment Discontinuation due to Efficacy
    - There were additional secondary endpoints specifically for subjects who discontinued treatment due to efficacy, including post-treatment relapse, sustained virologic response (HBeAg-positive), sustained serum HBV DNA suppression,

sustained HBeAg Loss (HBeAg-positive), sustained HBeAg seroconversion (HBeAg-positive), and sustained ALT normalization.

- Virologic Breakthrough
- Treatment-Emergent HBV Resistance
- Treatment Failure, including
  - Primary Treatment Failure
  - Secondary Treatment Failure

In the pivotal study, serum HBV DNA determinations were performed at the [redacted] reference laboratory through use of the COBAS Amplicor HBV Monitor™ assay [redacted], which utilizes polymerase chain reaction (PCR) methods and semi-automated sample readout technologies. For the analysis of serum HBV DNA, the lower limit of quantitation (LLOQ) with this assay was estimated to be approximately 300 copies/mL.

6.1.3 Study Design

The proposed dose of LdT was selected primarily on the basis of reductions in HBV DNA and safety and tolerability of the drug observed during NV-02B-001, a Phase 1-2 dose-escalation study conducted in adults with chronic hepatitis B and compensated liver disease. At the time of dose selection for the pivotal Phase 3 trial, 12-week data were available from the Phase 2b trial, NV-02B-003. These results showed that the 400mg and 600mg/day doses had very similar rates of efficacy (less than 0.3-0.5 log10 difference in HBV DNA reduction at 4 weeks), further solidifying the decision to select 600mg once daily as the LdT dose used in the pivotal trial. For more detailed review of the Phase 1 and Phase 2 studies, please refer to Dr. Jennifer Zheng's Clinical Pharmacology and Biopharmaceutics Review.

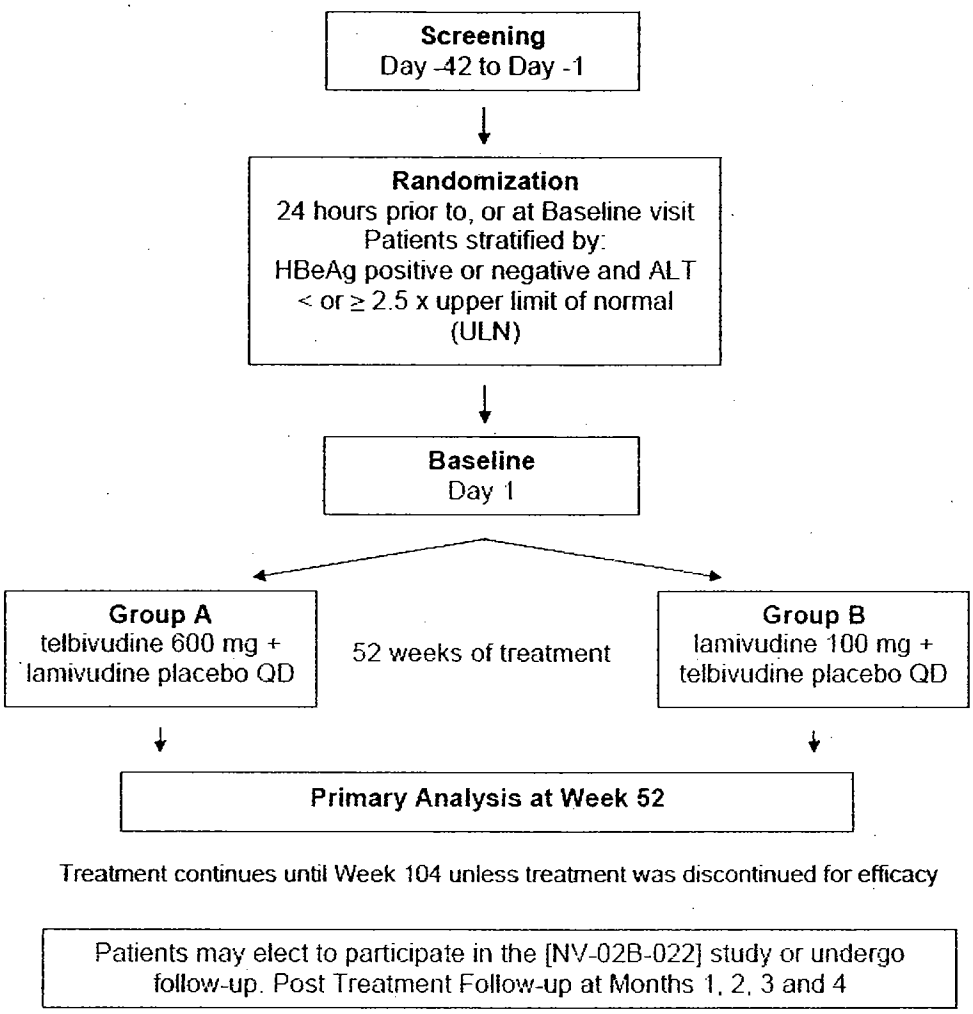
NV-02B-007 is an ongoing 104-week, randomized, double-blind, active-controlled, two-arm Phase 3 clinical trial designed to compare the efficacy and safety of LdT (600 mg/day) to LAM (100 mg/day). Subjects were stratified for treatment assignment according to hepatitis B e antigen status (positive versus negative) and alanine aminotransferase level (ALT <2.5 x ULN versus ALT ≥2.5 x ULN).

The primary efficacy analyses were scheduled to occur after all subjects completed 52 weeks and 104 weeks of study treatment. The foundation for the efficacy analysis in this document is the primary data analysis at Week 52. The analysis at Week 104 (study completion) will provide confirmatory, longer term data analysis.

A brief representation of the study design is shown below in Figure 6.1.3.A

Figure 6.1.3.A: Study Design for NV-02B-007

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



Source: Figure 9-1 in the NV-02B-007 Full Clinical Study Report

Subjects were HBeAg-negative or HBeAg-positive, nucleoside-naïve with compensated liver function. Other key inclusion criteria included: 16 years ≤ age ≤ 70, ALT ≥ (1.3-10) x ULN, liver biopsy within 12 months prior to randomization with histology compatible with chronic hepatitis B, screening serum HBV DNA level ≥ 6 log10 copies/mL, normal renal function, and compensated liver disease. Subjects with HCV, HDV, or HIV co-infection, one or more additional known primary or secondary causes of liver disease (other than HBV), clinical pancreatitis, a medical condition requiring prolonged or frequent use of systemic acyclovir, famciclovir, or corticosteroids, the use of potentially hepatotoxic drugs, or any other concurrent medical condition likely to limit compliance with the evaluations or confound the efficacy or safety observations (e.g. unstable angina, repeated myocardial infarctions (MI), seizure, active TB, renal insufficiency, uncontrolled diabetes) were excluded from the trial. Subjects with a history of treated malignancy (other than hepatocellular carcinoma (HCC)) who had been in complete remission off chemotherapy and without additional surgical intervention in the preceding three years were allowed in the trial.

Subjects with a history of HCC or findings suggestive of HCC, however, were required to have HCC ruled out prior to randomization. Subjects with current or recent history of alcohol or illicit drug abuse were excluded. Previous treatment with LAM, other investigational nucleoside or nucleotide analogues, IFN or any immunomodulatory therapy for HBV was an exclusion criterion. Recent (within 30 days of screening) or anticipated future anticoagulant therapy was an additional exclusion criterion. Female subjects were not allowed to be pregnant or breastfeeding and appropriate contraception was required of all participants.

The IVRS, besides being used to manage clinical trial material inventory, was used to randomly assign subjects to treatment groups in the LdT Phase 3 trial. Randomization was to occur in a 1:1 ratio across the two treatment groups (i.e., LdT 600 mg/day or LAM 100 mg/day), and be stratified according to two pre-stratification factors (HBeAg status, and ALT level). The Applicant reported that 62 Intention-To-Treat (ITT) subjects were assigned to the wrong stratum, and therefore incorrectly randomized, because their HBeAg status or ALT level was incorrectly entered into the IVRS. Among these 33 subects were incorrectly stratified for ALT results only, 28 for HBeAg results only and 1 subject was incorrectly stratified for both ALT and HBeAg results.

Continuation of blinded study treatment was based on results of the Week 52 evaluation. Among those who were HBeAg-positive at entry, subjects who exhibited Virologic Response (loss of detectable serum HBeAg with serum HBV DNA < 5 $\log_{10}$ copies/mL.) for at least 24 weeks were allowed to be discontinued from treatment (without study discontinuation). Among those who were HBeAg-negative at entry, subjects who achieved HBsAg loss at Week 52 or subsequently, documented on two successive study visits, were allowed to be discontinued from treatment (without study discontinuation). Subjects who experienced post-treatment relapse of HBV viremia (HBV DNA levels $\geq$6 $\log_{10}$ copies/ml on two or more consecutive visits, at least 2weeks apart, and associated disease parameters (e.g. elevated ALT levels to 2 x Upper Limit of Normal (ULN) or detectability of HBsAg)), could be retreated with blinded study drug.

Discontinuation from study was appropriate for any subject who developed signs suggesting a significant risk for hepatic disease progression, demonstrated by clinically-evident ascites, variceal or GI hemorrhage secondary to portal hypertension, hepatic encephalopathy, bacterial peritonitis and/or sepsis, decrease in serum albumin to < 3.0 g/dL, confirmed on two visits, or increase in serum bilirubin to ≥ 2 x ULN, attributed to liver disease other than obstructive biliary tract disease. Such findings were to be documented on two study visits whenever possible, including off-schedule study visits if necessary.

After the first 24 weeks of study treatment, subjects with persisting significant ALT elevation (e.g. greater than 2 x ULN) and with serum HBV levels $\geq$ 5 log10 copies/mL could be discontinued from study if they met either of the following two criteria:

- Severe ALT elevation with HBV viremia. At Week 24 or thereafter, ALT increases to 10 x ULN (and at least 2 x Baseline) on two or more visits over a period of at least 7 days; AND serum HBV DNA is $\geq$ 6 log10 copies/mL OR the serum HBV DNA pattern meets either of the virologic breakthrough definitions

  OR

- Persisting moderate ALT elevation with HBV viremia. Over 16 weeks of study observation at any time after Week 24, ALT is persistently elevated to levels $\geq$ 2 x ULN (and $\geq$ Baseline ALT level) AND serum HBV DNA is $\geq$ 6 log10 copies/mL OR serum HBV DNA pattern meets either of the virologic breakthrough definitions

The Applicant defined subjects who met either of the two criteria as treatment failures; these subjects could elect to continue on other therapies. Please see detailed discussion below in Section 6.1.5, Clinical Microbiology, on the use of virologic failure (HBV DNA ≥1,000 copies/mL on 2 consecutive occasions), instead of the Applicant's definition of treatment failure, described above, in the FDA analysis of data from NV-02B-007 to determine treatment success or failure.

As noted above in Section 6.1.2, General Discussion of Endpoints, the primary efficacy endpoint for NV-02B-007, Therapeutic Response, was defined as:

- Loss of detectable serum HBeAg or ALT normalization
  and
- Serum HBV DNA < 10^5 copies/ml by the COBAS Amplicor™ PCR assay.

The principal secondary efficacy endpoint, histologic improvement on liver biopsy at 52 weeks, was defined as at least a 2-point reduction in Knodell necroinflammatory score and no worsening of fibrosis. Secondary endpoints are outlined above in Section 6.1.2 and include composites of these and other endpoints.

The pivotal Phase 3 study, NV-02B-007, was designed to meet the Food and Drug Administration Modernization Act (FDAMA) of 1997 criteria for one adequate and well-controlled clinical trial (plus confirmatory evidence) using appropriate endpoints and efficacy analyses. The large sample size of NV-02B-007 and the representation of large numbers of subjects from the two key HBV subpopulations (HBeAg-positive and HBeAg-negative) essentially allowed the pivotal trial to provide as much data as two separate trials for the statistical efficacy and safety analyeses. The Phase 2b supporting trial data from NV-02B-003 and its follow-on trial, NV-02B-010, provided additional, required supportive evidence of LdT's antiviral efficacy.

The studies submitted with this NDA were not expected to address the response to LdT to special populations of subjects with decompensated liver disease or those who are post-liver transplantation.

MO Comments
The study design, including entry criteria for the pivotal (and supporting) studies are appropriate, based on the scientific evidence available when these studies were designed. As noted earlier in Section 6.1.2, current evidence would dictate a lower cut-off for the virologic response endpoint.

6.1.4 Efficacy Findings

Subjects who participated in the NV-02B-007 pivotal trial included a wide range of individuals with chronic HBV and compensated liver disease. Study participants were recruited from 20 countries in North America, Asia, Oceania (New Zealand and Australia) and Europe. Study demographics and baseline HBV disease characteristics for the pivotal trial are summarized below and again in Section 7.2.1.2, Demographics.

Table 6.1.4A: NV-02B-007: Subject Demographics

Demographic Characteristic, n (%)	**LdT**	**LAM**	**Total Subjects**
Received Study Drug	680	687	1367
Age (years)			

Median	34	35	34
Min, Max	16, 68	16, 68	16, 68
Gender, n (%)			
Male	507 (74.6)	529 (77)	1036 (75.8)
Female	173 (25.4)	158 (23)	331 (24.2)
Race, n (%)			
Asian[a]	525 (77.2)	515 (75)	1040 (76.1)
Caucasian	98 (14.4)	111 (16.2)	209 (15.3)
African/African-American	7 (1)	10 (1.5)	17 (1.2)
Middle Eastern/Indian Subcontinent	14 (2.1)	11 (1.6)	25 (1.8)
Hispanic/Latino	4(0.6)	8(1.2)	12(0.9)
Other races	32 (4.7)	32 (4.7)	64 (4.7)
Geographic Region			
Asia	445(65.4)	408(59.4)	853(62.4)
North America	74(10.9)	90(13.1)	164(12.0)
Europe	97(14.3)	108(15.7)	205(15.0)
Oceania	64(9.4)	81(11.8)	145(10.6)

Source: Medical Officer Review of electronic datasets, DEMOG, and Table 10-1 in NV-02B-007 Full Clinical Study Report.

[a] Includes Chinese, Korean, Thai, Japanese, Vietnames, Filipino, Malay, and other Asian.

MO Comments

According to the FDA Guidance for Industry on the Collection of Race and Ethnicity Data in Clinical Trials,, the following minimum choices should be offered for racial/ethnic categorization in clinical trials conducted both inside and outside of the United States: (1) American Indian or Alaska Native, (2) Asian, (3) Black or African-American, (4) Native Hawaiian or Other Pacific Islander, and (5) White. The guidance notes that the category, "White" can reflect origins in Europe, the Middle East, or North Africa. The Applicant, however, has included trial subjects of Middle Eastern descent in a separate category Middle Eastern/Indian subcontinent.

For this review, the demographic data was analyzed according to the racial/ethnic categorization specified by the Applicant. These analyses showed that the distributions of age, gender, race, height and weight were similar in LAM and LdT Subjects. Approximately 75% of the subjects were males, 75% of the subjects were Asian and 15% were Caucasian. There were very few African American, Hispanic or Other subjects enrolled, however. For African/African-Americans and Hispanics, in particular, there was a significant underrepresentation of this group in the clinical trial compared to the increased prevalence of chronic HBV in African Americans in the U.S. population.

Table 6.1.4.B: NV-02B-007: Baseline HBV Disease Characteristics-ITT population

	HBeAg-positive		**HBeAg-negative**	
Characteristic	**LdT** (n=458)	**LAM** (n=463)	**LdT** (n=222)	**LAM** (n=224)
Median Baseline HBV DNA (log_{10} copies/ml) (range)	9.51 (3.8, 16.0)	9.57 (3.6, 16.1)	7.66 (3.0, 13.0)	7.42 (3.7, 12.1)
Median Baseline ALT (IU/L) (range)	110.5 (19, 1137)	111.0 (25, 1133)	99.0 (31, 569)	98.5 (12, 982)

Source: Table 11-11, 11-12, 11-14, and 11-15 from the NV-02B-007 Full Clinical Study Report

The modified ITT (mITT) population for histologic analyses in NV-02B-007 included all subjects with evaluable pretreatment liver histology slides. As shown in Table 6.1.4 C below, both treatment arms exhibited similar baseline liver histology scores within HBeAg-positive and HBeAg-negative subpopulations.

Table 6.1.4.C: NV-02B-007: Mean Liver Histology Scores at Baseline-mITT

	HBeAg-positive		HBeAg-negative	
Characteristic	**LdT** (n=439)	**LAM** (n=433)	**LdT** (n=212)	**LAM** (n=218)
Knodell Necroinflammatory Score (0-18)	7.4	7.3	7.3	7.6
Knodell Fibrosis Score (0-4)	1.5	1.6	1.7	1.9
Ishak Fibrosis Score	2.1	2.2	2.3	2.5

Source: Table 11-18 from the NV-02B-007 Full Clinical Study Report

Most subjects were HBV geonotype C at baseline, particularly in the HBeAg-positive subgroup. HBV genotype B was also very common among study subjects.

MO Comments
There were no significant differences in the distribution of HBV serologic markers or baseline liver histology in LAM and LdT HBeAg-positive and HBeAg-negative subjects. The distribution of HBV genotypes appeared to be comparable in the two treatment groups. Genotypes A (more prevalent in North America), D, E, F, and H were underrepresented in the pivotal trial.

The primary efficacy analysis and selected secondary analyses were reviewed in detail by Dr. Fraser Smith in his Statistical Review of this NDA. The discussion of efficacy included below is derived from the Medical Officer's Review of Dr. Smith's analyses and the Applicant's analyses provided in the original NDA submission.

Primary Efficacy Analysis
The primary efficacy endpoint for the pivotal Phase 3 study, NV-02B-007, was Therapeutic Response, defined as loss of detectable serum HBeAg or ALT normalization and serum HBV DNA $< 10^5$ copies/ml (by the COBAS Amplicor™ PCR assay). The efficacy analyses for the primary endpoint of Therapeutic Response and the principal secondary endpoint, Histologic Response, were conducted using a multi-step process to control for Type1 error. First, an analysis of non-inferiority of the 2 treatment arms was conducted, followed by a second step analysis, if LdT proved to be non-inferior, to evaluate the superiority of LdT compared to LAM. Both the DAVP and the Applicant agreed to a hierarchical fixed hypothesis testing approach for the efficacy endpoints and Therapeutic Response was the first endpoint in the testing algorithm. The ordering of these endpoints is reflected below in Table 6.1.4.I. It was necessary to meet non-inferiority for Therapeutic Response before evaluating the superiority of LdT compared to LAM or testing the next endpoint, Histologic Response.

Table 6.1.4.D: NV-02B-007: Primary efficacy endpoint (TR at Wk 52) by treatment group and HBeAg status - ITT and EE populations

Group	**LdT** n/N (%)	**LAM** n/N (%)	**95.68% CI***	**p-value†**
ITT population				
HBeAg-positive	345/458 (75.3)	310/463 (67.0)	2.4, 14.2	0.0047

HBeAg-negative	167/222 (75.2)	173/224 (77.2)	-10.2, 6.1	0.6187
EE population				
HBeAg-positive	334/434 (77.0)	299/445 (67.1)	4.0, 15.9	0.0007
HBeAg-negative	174/228 (76.3)	180/223 (80.8)	-12.3, 3.3	0.2461

Source: Table 11-21 of the NV-02B-007 Full Clinical Study Report
*CI adjusted for multiple comparison to test treatment/antigen status interaction with an α level of 0.0432
†Treatment group differences controlled for randomization strata: difference between proportions for categorical variables
EE= Efficacy Evaluable Population
Non-inferiority Margin=-15%

The Applicant found that LdT was non-inferior to LAM in both HBeAg subpopulations for the primary efficacy endpoint, Therapeutic Response. The Applicant also claimed superiority of LdT relative to LAM for Therapeutic Response among subjects in the HBeAg-positive subgroup. Compared to LAM subjects, a significantly greater proportion of LdT subjects (75%) than LAM subjects (67%) in the HBeAg-positive subpopulation experienced a Therapeutic Response at Week 52 in the ITT population (p=0.0047). The FDA statistical analysis confirmed the Applicant's finding of non-inferiority for LdT in both the ITT and EE populations. Using the 3-step statistical test procedure described in Lu and Huque [Biometrical Journal 43 (2001) 7, 909-923], Dr. Smith also conducted separate analyses in the HBeAg-positive and HBeAg-negative populations. His analysis also showed found statistical significance in the TR endpoint among HBeAg-positive subjects, favoring LdT.

Since the Applicant's analyses, shown above in Table 6.1.4.D, did not correct for the IVRS misclassification of subjects, the Statistical Reviewer re-analyzed the primary efficacy data, with the subjects assigned to the correct HBeAg subpopulations, and confirmed the determination of non-inferiority and lack of superiority for LdT in both HBeAg subpopulations.

MO Comments
Despite the statistically significant difference in TR favoring LdT among the HBeAg-positive subjects, this result was not replicated among HBeAg-negative subjects. NV-02B-007 was structured to allow each HBeAg subgroup to be analyzed separately and function similar to an individual trial. Since superiority was only demonstrated in one subgroup (equivalent to one trial), superiority cannot be claimed for the overall study without replication of the efficacy outcomes in a second trial (or a second subpopulation). The Division is not going to grant LdT a claim of superiority of LdT over LAM for the primary efficacy endpoint. Replication of the finding of superiority in another study among HBeAg-positive subjects would be necessary for the Division to consider a claim of superiority for LdT over LAM in the future.

As noted in Dr. Fraser Smith's Statistical Review, the Applicant performed sensitivity analyses for missing data by excluding subjects with missing values (Tables 14.2.1.30, 14.2.1.31, 14.2.1.32 and 14.2.1.33 of the Clinical Study Report). The Applicant also computed odds ratios for treatment effects in both the ITT and EE populations (Tables 14.2.2.3, 14.2.2.4, 14.2.2.5 and 14.2.2.6 of the Clinical Study Report). The Statistical Reviewer also achieved parallel results for the primary efficacy endpoint using proc freq in SAS. He also conducted the Breslow-Day tests of homogeneity of the odds ratio across both HBeAg subpopulations and found that they were statistically significant at the pre-specified α=0.15 level (p=0.0503).

Subgroup Analyses for Primary Efficacy Endpoint
The Statistical Reviewer also performed a series of subgroup analyses based on selected demographic (gender, race, age, geography) and baseline disease characteristics (ALT, HBeAg

status, genotype, HBV DNA). The treatment effect for the primary endpoint was generally comparable for most covariates, but there were subgroups within the analyses for whom LdT was shown to be superior to LAM. These findings do not affect the treatment recommendations or the LdT labeling claim of non-inferiority. There were also subgroups within the analysis for which LdT did not meet non-inferiority criteria compared to LAM. These include:

- HBeAg-negative female subjects
- Subjects older than 50 years of age
- African-American and Hispanic subjects
- HBeAg-negative subjects with baseline ALT <2.5 × ULN
- HBeAg-negative subjects with baseline genotype B or other genotype

In particular, when Therapeutic Response was analyzed by baseline ALT stratification category, the non-inferiority results for LdT were demonstrated in the HBeAg-positive subjects in both ALT strata (ALT < 2.5 X ULN and ALT $\geq$ 2.5 X ULN) and in the HBeAg-negative subjects with baseline ALT < 2.5 X ULN. Superiority of LdT over LAM was noted only in the HBeAg-positive subjects with baseline ALT < 2.5 X ULN. Across both treatment groups, however, the scope of the treatment effect appeared to be somewhat better for subjects in the high ALT/HBeAg-positive and high ALT/HBeAg-negative strata, when compared to the subjects in the low ALT strata.

In addition, when the Statistical Reviewer examined geographic region for a possible treatment effect, the result from the Breslow-Day for testing the homogeneity of treatment effects was small enough, but not statistically significant, to suggest the potential for a treatment effect by geographic region interaction. LdT subjects in the Asia-Pacific region and Canada appeared to have a slightly better treatment response than LAM subjects, whereas LdT subjects in Europe and the US had a slightly worse response than LAM subjects. The treatment effect was largely driven by the results from the Asia-Pacific region and the DSI site inspections (Taiwan, New Zealand, Austrailia, Thailand) there did not reveal significant irregularities.

MO Comments
Given the disparity in the size of study site populations in various geographic regions, it is difficult to draw conclusions regarding the impact of geography on treatment response. There were relatively few subjects in the USA or Europe compared to the Asia-Pacific region. It is reassuring that the Asia-Pacific sites inspected by DSI did not reveal any irregularities.

The Applicant and the FDA Statistical Reviewer also examined the primary efficacy endpoint in the "interferon-eligible" population, which represented 67% of the HBeAg-positive population (baseline ALT $\geq$ 2 × ULN) in the ITT population. As in other groups of HBeAg-positive subjects in the ITT population, superiority was demonstrated for the Therapeutic Response endpoint.

MO Comments
These exploratory subgroup analyses do not have sufficient power to draw meaningful conclusions, but they do have descriptive value. The subgroups in whom non-inferiority was not met for LdT when compared to LAM reflect very small subsets of the study population. It is difficult to know if there are treatment implications for these particular subject populations.

Given the prevalence of chronic HBV among African-Americans and Hispanic-American, the limited representation of these populations in NV-02B-007 and the absence of a treatment effect among those subjects, additional studies to confirm the efficacy of LdT are warranted in these populations.

In addition, the potential for a treatment effect by geographic region may be masking a treatment effect by genotype, given the diversity of genotypes across geographic regions.

There is insufficient information to determine the role of LdT relative to IFN among interferon-eligible subjects with chronic HBV. Head-to-head trials have not been conducted between LdT and interferon.

Secondary Efficacy Analyses

In the SAP, the order of analysis for the secondary efficacy endpoints was specified to control for overall Type 1 error. Both the DAVP and the Applicant agreed to this hierarchical fixed hypothesis testing approach for the primary and the secondary endpoints in NV-02B-007. The ordering of these endpoints is reflected below in Table 6.1.4. I. It was necessary for subjects within the particular HBeAg subpopulation to meet non-inferiority for all prior endpoints before testing the next endpoint. If non-inferiority was met, then the endpoint could also be tested for superiority. The secondary efficacy analyses were rooted in this hierarchical fixed hypothesis testing approach.

As noted above in Section 2.5, Presubmission Regulatory Activity, and in the SAP, Histologic Response was the most important secondary efficacy endpoint. Histologic Response was defined as at least a 2-point reduction in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score. The effect of LdT compared to LAM was also examined for a host of other secondary endpoints measuring virologic, serologic and biochemical responses. The Statistical Reviewer's analysis showed that a significantly higher proportion of LdT subjects than LAM subjects met the endpoints listed below:

- Histologic Response (HBeAg-positive)
  - Only non-inferiority was demonstrated for LdT in the HBeAg-negative population.
- At least 2-point Improvement in Knodell Scores (HBeAg-positive)
  - Only non-inferiority was demonstrated for LdT in the HBeAg-negative population
- Mean HBV DNA reduction from baseline at Weeks 24 and 52 (both HBeAg subpopulations)
- HBV DNA levels of at least 5 $\log_{10}$ copies/mL at Week 52 (both HBeAg subpopulations)
- PCR-nondetectable HBV DNA at Week 52 (both HBeAg subpopulations)
- Earlier time to maintained undetectable HBV DNA(both HBeAg subpopulations)
- Primary, secondary and total treatment failure[21] rates (HBeAg-positive subpopulation)
  - LdT was also favored in the HBeAg-negative subpopulation although treatment differences were only statistically significant for total failures.

Secondary Efficacy Analyses: Histologic and Fibrosis Response

Table 6.1.4.E: NV-02B-007: Histological Improvement and Change in Ishak Fibrosis Score at Week 52

[21] Please see Clincial Microbiology in Section 6.1.5 for discussion regarding the use of Microbiology Reviewer's definition of virologic failure (for consistency with ADV and ETV reviews) instead of the Applicant's definition of treatment failure in her review.

	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.

Both the FDA Statistical Reviewer and the Applicant found that a significantly greater proportion of HBeAg-positive LdT subjects in the mITT population[22] had a Histologic Response at Week 52 (non-inferiority Margin=-15%), compared to HBeAg-positive LAM subjects (p-value =0.0105; 95.68% CI =2.0, 14.7). Among HBeAg-negative subjects, the Histologic Response of LdT subjects was non-inferior to the response of LAM subjects (p-value=0.8994; 95.68% CI =-8.3, 9.5).[23]

In addition to Knodell fibrosis scoring, Ishak fibrosis scoring was conducted. An improvement in the Ishak fibrosis score was defined as a 1-point or greater reduction in Ishak fibrosis score between the baseline biopsy and the follow-up biopsy (Wk 52).[24] The Change in Ishak Fibrosis Score among HBeAg-positive LdT subjects did not meet the pre-specified non-inferioritiy criterion because the lower limit of the 95% confidence interval was greater than the prespecified non-

[22] The modified ITT (mITT) population for histologic analyses in NV-02B-007 included all subjects with evaluable pretreatment liver histology slides.
[23] P-values and confidence intervals are based on the Applicant's analyses.
[24] The statistical reviewer summarized Ishak Fibrosis Score using subjects with baseline Knodell Necroinflammatory Scores of at least 2 points in the modified Efficacy Evaluable (EE) population for consistency with the approach used in previous reviews of ETV and ADV. There results were not much different from those obtained by the Applicant using subjects with a prespecified baseline total HAI score >3. There were no statistically significant treatment group differences in either HBeAg subpopulation among subjects with high baseline Ishak Fibrosis scores (≥3) (p=0.61 in the HBeAg-Positive subpopulation and p=0.74 in the HBeAg-Negative subpopulation).

inferiority margin of 8% (p-value =0.0774; 95 % CI = -12.3, 0.6). Also, the p-value for the difference between LdT and LAM in the HBeAg-positive subjects was almost statistically significant in favor of LAM. There were no statistically significant differences in the Ishak fibrosis score for the HBeAg-negative subjects (p-value =0.7209; 95 % CI = -7.7, 11.1).

MO Comments

While LdT's Histoloic Response, in HBeAg-positive subjects only, was superior to LAM, the DAVP will not grant a claim of superiority to LdT for Histologic Response because the superiority results were not replicated in the study's other subject population (HBeAg-negative subjects). For labeling purposes, LdT is considered non-inferior to LAM for the key secondary efficacy endpoint, Histologic Response.

Also, it is unclear why LdT did not meet non-inferiority criteria for fibrosis among HBeAg-positive subjects. Anti-HBV therapy is usually expected to help slow down the progression of fibrosis. As the Applicant noted in the NV-02B-007 study report, longer periods of histologic assessment might be needed to observe any LdT-related advantage on fibrosis. In their respective labels, ADV showed a 34% improvement in the Ishak fibrosis score at Week 48 (compared to placebo with 19% improvement) and ETV showed a 39% improvement in the Ishak fibrosis score at Week 48 (compared to LAM which had 35 % improvement). While there are significant limitations to cross-study comparisons, it is reassuring that even though LdT did not meet non-inferiority criteria relative to for an improvement in the Ishak fibrosis score compared to LAM in NV-02B-007, the 41% improvement associated with LdT is still on par with the findings in the ETV and ADV pivotal studies.

Secondary Efficacy Analyses: Antiviral Efficacy

LdT was found to be non-inferior to LAM on study measures of antiviral efficacy including quantitative reduction in serum HBV DNA, rate of reduction in serum HBV DNA to less than 5 $\log_{10}$ copies/mL, and reduction in serum HBV DNA to PCR-nondetectable levels, in both HBeAg-positive and HBe-Ag-negative populations.

Antiviral Efficacy: Mean HBV DNA Reduction

Table 6.1.4.F: NV-02B-007: HBV DNA reduction ($\log_{10}$ copies/mL) from Baseline at Weeks 24 and 52 - ITT population

	HBeAg-positive			**HBeAg-negative**		
Time point	**LAM**	**LdT**	p-value	**LAM**	**LdT**	p-value
	N=463	N=458		N=224	N=222	
Week 24	n=453	n=450		n=221	n=222	
mean (SE)	-5.9 (0.09)	-6.4 (0.08)	<0.0001	-4.8 (0.11)	-5.2 (0.11)	0.0023
median	-6.0	-6.5		-4.7	-4.9	

Week 52	n=444	n=443		n=219	n=219	
mean (SE)	-5.5 (0.12)	-6.4 (0.09)	<0.0001	-4.4 (0.14)	-5.2 (0.13)	<0.0001
median	-5.9	-6.7		-4.5	-5.0	

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

The FDA Statistical Reviewer confirmed that mean HBV DNA reductions from baseline were significantly larger for LdT subjects in both HBeAg subpopulations at Weeks 24 and 52.

Antiviral Efficacy: HBV DNA Reduction

Table 6.1.4.G: NV-02B-007: Proportion of subjects who achieved specific HBV DNA levels at Week 52, by HBeAg status – ITT population

	HBeAg-positive		**HBeAg-negative**	
Time point	**LdT** (N=458)	**LAM** (N=463)	**LdT** (N=222)	**LAM** (N=224)
Week 52	n=443	n=444	n=219	n=219
<3 log10	308 (69.5)	219 (49.3)	198 (90.4)	174 (79.5)
<4 log10	351 (79.2)	279 (62.8)	206 (94.1)	186 (84.9)
<5 log10	403 (91.0)	337 (75.9)	211 (96.3)	196 (89.5)
≥5 log10	40 (9.0)	107 (24.1)	8 (3.7)	23 (10.5)

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

Compared to LAM, the proportion of subjects with HBV DNA levels of less than 5 $\log_{10}$ copies/mL at Week 52 (and week 24) was greater among LdT subjects, showing a higher degree of antiviral reduction among LdT subjects.

Antiviral Efficacy: Non-Detectable HBV DNA by PCR

Table 6.1.4.H: NV-02B-007: Proportion of Subjects with PCR-nondetectable HBV DNA by study visit, by HBeAg status - ITT population

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

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

As noted above in Table 6.1.4.H, LdT has significantly higher proportions of subjects with PCR-nondetectable HBV DNA at Weeks 24 and 52. Also, both HBeAg subpopulations on LdT showed an earlier time to maintained PCR-nondetectable HBV DNA[25] than LAM subjects. The proportion of subjects with a maintained PCR-Nondetectable HBV DNA[26] Response was only slightly lower than the percentage of all subjects with PCR-nondetectable HBV DNA at Week 52.

Secondary Efficacy Analyses: ALT Normalization

ALT normalization was defined as ALT normalization on two consecutive visits for subjects with an elevated ALT (> 1.0 x ULN) at baseline. Approximately 76% of HBeAg-positive subjects and 77% of HBeAg-negative subjects in the ITT population achieved ALT normalization by Week 52. Proportionally more HBeAg-positive subjects on LdT achieved ALT normalization compared to LAM, whereas a greater proportion of HBeAg-negative subjects on LAM achieved ALT normalization compared to LdT. LdT did not demonstrate superiority over LAM for ALT normalization.

Secondary Efficacy Analyses: Virologic Breakthrough at Week 48 and Virologic Response

The percentages of LdT subjects with Virologic Breakthough, as defined by the Applicant, and HBV Resistance, as defined by the Applicant, were significantly lower than the corresponding percentage of LAM subjects for both HBeAg-positive and HBeAg-negative subpopulations.

However because Virologic Breakthrough was pre-specified to be tested after ALT Normalization in the hierarchical fixed hypothesis of testing and because LdT was not superior to LAM for ALT normalization , then LdT could not be found to be superior to LAM for Virologic Breakthrough or any of the endpoints that followed ALT normalization on the testing hierarchy (e.g. virologic response, HBeAg seroconversion, HBeAg loss, change in Ishak Fibrosis Score, primary treatment failure, HBsAg loss and HBsAg seronconversion).

LdT can be considered non-inferior to LAM, however, because there was a statistically significant difference favoring LdT for the Virologic Breakthrough endpoint (i.e., the lower bound of the confidence interval was greater than 0, the smallest possible non-inferiority margin).

MO Comments
While the FDA and Applicant's assessment of antiviral efficacy supports the finding that LdT has a higher reduction in viral load relative to LAM, the rules of the hierarchical fixed testing hypothesis described above result in a finding of non-inferiority for LdT relative to LAM. The Microbiology Reviewer conducted similar analyses at Week 52, using slightly different endpoint definitions (for consistency with ADV and ETV reviews). Please the Microbiology Review by Dr. Sung Rhee and Section 6.1.5, Clinical Microbiology, of this review, for further details.

[25] Time to Maintained Undetectable HBV DNA was defined as the time from Baseline to the first of the two consecutive visits for patients who met the Maintained HBV Non-Detectable Endpoint.
[26] Maintained PCR non-detectable HBV DNA (Maintained PCR Negative) was defined as: HBV DNA < 300 copies/mL for at least two consecutive visits and at the patient's last treatment visit with no two intervening consecutive visits where a patient had HBV DNA ≥ 300 copies/mL.

Secondary Efficacy Analyses: Serologic Endpoints (HBeAg responses)

Serologic Endpoints: HBeAg Loss and seroconversion.

The rates of HBeAg loss and seroconversion were slightly higher among LdT subjects than LAM subjects, but the differences were not statistically significant. LdT did meet criteria for non-inferiority for both HBeAg loss and HBeAg seroconversion (no 95% confidence interval less than -5.5).

As noted earlier in this section, LdT did not meet non-inferiority criteria for the Change in Ishak score in the HBeAg-positive subpopulation, so as a result, using the fixed hierarchy of testing, LdT cannot be considered non-inferior for the endpoint of primary treatment failure in this subpopulation (see ordering associated with the hierarchical fixed hypothesis of testing below in Table 6.14.I). There was not a statistically significant difference between LdT and LAM for this endpoint in the HBeAg-negative subpopulation.

Further discussion of the remaining secondary endpoints examined under the hierarchical fixed hypothesis testing can be found in the Statistical Review by Dr. Fraser Smith. Table 6.1.4.I outlines modifications to the Applicant's conclusions based the outcomes of Dr. Smith's analyses.

Table 6.1.4.I: NV-02B-007: Results of hierarchical fixed hypothesis testing of primary and secondary efficacy endpoints

Efficacy Endpoint*		Subpopulations	
		HBeAg-positive	HBeAg-negative
1	**Therapeutic Response**	S	NI
2.1	**Histologic Response**	S	NI
2.2	**Serum HBV DNA Reduction**	S	~~S~~[1] NI

2.3	**Serum HBV DNA Undetectable**	S	~~S~~[1] NI
2.4	**ALT Normalization**	NI	NI
2.5	**Virologic Breakthrough at Wk 48**	~~S~~[1] NI	~~S~~[1] NI
2.6	**Virologic Response**	NI	/
2.7	**HBeAg Seroconversion**	NI	/
2.8	**HBeAg Loss**	NI	/
2.9	**Change in Ishak Fibrosis Score**	~~NI~~[2]	NI
2.10	**Primary Treatment Failure**	~~S~~[1]	Unable to achieve superiority
2.11	**HBsAg Loss**	~~NI~~[3]	/
2.12	**HBsAg Seroconversion**	~~NI~~[3]	/

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

MO Comments
LdT was found to be superior to LAM in the HBeAg-positive subpopulation and non-inferior to LAM in the HBeAg-negative subpopulation for the following antiviral efficacy endpoints: Serum HBV DNA Reduction, and Serum HBV DNA Undetectable. LdT was non-inferior to lamivudine in both HBeAg subpopulations for Virologic Breakthrough at Week 48. Also, LdT was non-inferior to LAM in the HBeAg-positive subpopulation for Virologic Response. Due to the hierarchy of fixed hypothesis testing, LdT was not found to be superior to LAM for the HBeAg-positive subpopulation, since Virologic Breakthrough at Week 48 and Primary Treatment Failure were after ALT Normalization in the hierarchy of fixed hypothesis testing, and telbivudine was not shown to be superior to lamivudine with respect to ALT normalization, it is not valid to claim that telbivudine is superior to lamivudine for Virologic Breakthrough or Primary Treatment Failure.

In summary, LdT was found to have antiviral efficacy that was non-inferior to that provided by LAM. The Division will consider a claim of superiority for LdT relative to LAM if the superiority achieved in the HBeAg-positive subpopulation can be replicated in an additional trial. Future composite efficacy endpoints in HBV treatment trials are likely to include a more stringent virologic criterion (e.g. PCR non-detectable HBV DNA).

Secondary Efficacy Analyses: Interferon-Eligible Population

The Applicant and the FDA Statistical Reviewer also conducted analyses of secondary efficacy endpoints in the "interferon-eligible" population. As with other HBeAg-positive ITT subjects, superiority was demonstrated for the first four endpoints in the hierarchy: histologic response, HBV DNA decrease and PCR-nondetectable.

MO Comments
There is insufficient information to determine the role of LdT relative to IFN among interferon-

eligible subjects with chronic HBV. Head-to-head trials have not been conducted between LdT and interferon.

The following conclusions can be drawn, based upon the findings of the Applicant and the FDA Statistical Reviewer:

- LdT was superior to LAM in the HBeAg-positive subpopulation and non-inferior to LAM in the HBeAg-negative subpopulation for the following secondary endpoints: Histologic Response (Key Secondary Endpoint), Serum HBV DNA Reduction, and Serum HBV DNA Undetectable (see Table 6.1.4.F).

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

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

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

For a more detailed discussion on the FDA analysis of the primary and secondary efficacy endpoints, please refer to Dr. Fraser Smith's Statistical Review. For a more detailed discussion of the FDA analysis of virologic outcomes, please refer to Dr. Sung Rhee's Microbiology review.

MO Comments
Based on the Statistical Reviewer's analysis, the Applicant cannot claim superiority for any secondary endpoints in the hierarchy unless LdT was found to be superior to LAM for any previous endpoints. As a consequence, there were fewer secondary endpoints that achieved superiority in either subpopulation than the Applicant initially proposed. Given the use of a composite primary efficacy endpoint, however, the non-inferiority of histologic response provides confirmatory support for the non-inferiority seen with the primary efficacy endpoint. The statistical reviewer made corrections in Table 6.1.4.I by crossing a line through the Applicant's claim of non-inferiority (NI) or superiority (S) and providing a rationale in the footnotes.

To date, there have been no direct comparisons of LdT and ETV or ADV for the treatment of chronic HBV, although there are studies in progress. The registrational studies for ADV employed a placebo rather than active control and a different study design with a different primary endpoint and, therefore, are difficult to compare to the LdT pivotal study. However, some of the ETV Phase 3 studies also evaluated both HBeAg-positive and HBeAg-negative, nucleoside-naïve subjects and used LAM as an active control. The ETV Phase 3 studies, like ADV, used Histologic Response as the primary efficacy endpoint. The ADV product label states that 53% of HBeAg positive, nucleoside-naive subjects receiving ADV and 64% of HBeAg negative subjects receiving ADV achieved Histologic Improvement at Week 48 compared to 25% and 35%, respectively, of subjects receiving placebo. From these data it is impossible to conclude whether LdT will provide a treatment benefit compared to ADV. Table 2 in the ETV product label demonstrates that 72% of HBeAg-positive, nucleoside-naive subjects receiving ETV and 70% of HBeAg-negative subjects receiving ETV achieved histologic improvement at Week 48 compared to 62% and 61%, respectively, of subjects receiving LAM. In the case of LdT, Table 6.1.4.E shows that 69% of HBeAg positive, nucleoside-naive subjects receiving LdT and 69% of HBeAg negative subjects receiving LdT achieved histologic improvement at Week 52 compared to 60% and 68%,

respectively, of subjects receiving LAM.

6.1.5 Clinical Microbiology

The Applicant has conducted *in vitro* and clinical evaluations of the microbiologic properties of LdT, including the potential for the development of resistance to LdT. Subjects in NV-02B-007 were monitored for the emergence of resistance to their HBV. Please refer to the Clinical Microbiology Review conducted by Dr. Sung Rhee for a complete review of the microbiology data. A summary of her conclusions is provided below.

Key non-clinical microbiology findings from Dr. Rhee's Microbiology Review include:

- LdT was not effective against other human viruses tested including human immunodeficiency virus (HIV-1).
- LdT-TP did not inhibit human cellular DNA polymerases α, β, or γ in biochemical reactions at concentrations up to 100 μM.
- LdT was not cytotoxic to numerous cell lines of human and other mammalian origin at the highest concentration tested. Also at concentrations of >10 μM, LdT did not inhibit the growth of human bone marrow progenitor cells.
- No mitochondrial toxicity was observed in studies conducted in the hepatoma cell line, HepG2, cells treated with LdT at concentrations up to 10 μM. These studies included analysis of lactic acid production, mtDNA content, and determination of changes in morphology (e.g., loss of cristae, matrix dissolution and swelling, and lipid droplet formation) of mitochondrial ultrastructure.
    - Under conditions of the assays, the HepG2 cell doubling time was approximately 1.43 days. Lactic acid levels were measured following 4-day drug exposure (~5.7 cell doublings). Mitochondrial DNA content and ultrastructure were assessed following 14-day drug exposure (~20 cell doublings). Of note, the cells were proliferating over the 14-day culture period and the cell doubling time was linear.
- LdT exerted additive antiviral effects when combined with ADV in a stably transfected cell line, HepG2 49-29. No evidence of cytotoxicity or antagonism was observed at the tested concentrations.
- Cell-based drug combination studies demonstrated that LdT did not enhance or reduce the antiviral efficacy of all seven FDA-approved HIV NRTIs against HIV-1. HIV NRTIs didanosine and stavudine exhibited no antagonistic effect on the cell culture antiviral activity of LdT against HBV.

MO Comments

An important adverse event of myopathy was found among LdT subjects (see Section 7.1.3.3, Other Significant Adverse Events.) Mitochondrial toxicity has been associated with some drugs in the nucleoside analogue class. It is reassuring that the in vitro analyses of the impact of LdT exposure on rapidly dividing HepG2 cells did not show evidence of mitochondrial toxicity. Additional analyses are needed, however, including in vitro testing for mitochondrial toxicity in growing muscle cells, cell lines and primary cells, and primary hepatocytes with appropriate controls to validate the results. Please see Dr. Sung Rhee's review for these and other non-clinical microbiology post-marketing commitments.

Key clinical microbiology findings from Dr. Rhee's Microbiology Review are described below:

Table 6.1.5 A: NV-02B-007: Summary of Virologic Findings

	HBeAg-positive		HBeAg-negative	
	LdT	**LAM**	**LdT**	**LAM**
Mean Serum HBV DNA Reduction at Wk 52 (log_{10} copies/mL)	6.44± 2.01	5.46± 2.55	5.18 ± 1.90	4.37 ± 2.08
Serum HBV DNA <1,000 copies/mL and maintained to Wk 52	65.4% (291/445)	45.9% (209/455)	91.1% (214/235)	77.6% (180/232)
Serum HBV DNA clearance to PCR nondetectable levels (≤300 copies/mL HBV DNA) and maintained to Wk 52	57.8% (257/445)	37.8% (172/455)	88.5% (208/235)	70.7% (164/232)
Virologic failure[27] (HBV DNA ≥1,000 copies/mL at Wk 52)	33.7% (145/430)	53.2% (233/438)	8.4% (19/227)	21.5% (48/223)
Virologic rebound[28] (≥1 log_{10} increase of HBV DNA from nadir while on therapy)	7.9% (34/430)	23.5% (233/438)	4.9% (11/227)	16.6% (37/223)
PCR Non-detectable (HBV DNA < 300 copies/mL)	57.8% (257/445)	37.8% (172/455)	88.5% (208/235)	70.7% (164/232)

Source: Table 11, FDA Microbiology Review

LdT showed greater serum HBV DNA reduction, greater proportions of subjects achieving HBV DNA suppression (to <1,000 copies/mL) and viral clearance to PCR non-detectable levels (<300 copies/mL), and reduced virologic failure and treatment-emergent virologic rebound, compared to LAM in both HBeAg-positive and HBeAg-negative subjects. LdT did not meet criteria for superiority based on prespecified requirements of the hierarchical fixed testing hypothesis.

In her analyses, the Microbiology Reviewer, Dr. Sung Rhee, modified the Applicant's definitions of virologic breakthrough (defined as virologic rebound by reviewer) and primary treatment failure (defined as virologic failure by the reviewer) to be consistent with the updated definitions used in the analyses of ADV and ETV for FDA approval. In addition, Dr. Rhee used an "as-treated" analysis to determine the endpoints of virologic rebound and virologic failure, excluding subjects who discontinued study prior to Week 16 from the analysis. When a subject discontinues study earlier than 16 weeks, it is more difficult to accurately assess these endpoints.[29] For these reasons, the outcomes of the analyses by the Microbiology Reviewer are reflected in the LdT label.

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[27] The definition of virologic failure used by the Microbiology Reviewer, Dr. Sung Rhee is the failure to achieve HBV DNA viral suppression defined as HBV DNA < 10^3 copies/mL on 2 consecutive visits at Wk 52, which differs from the definition used by the Applicant to reflect a similar concept (primary treatment failure defined as the failure to achieve HBV DNA viral suppression defined as HBV DNA < 10^5 copies/mL on 2 consecutive visits).

[28] The definition of virologic rebound used by the Microbiology Reviewer, Dr. Sung Rhee is HBV DNA ≥1 log_{10} increase from nadir on 2 consecutive visits while on therapy, which differs from the definition used by the Applicant to reflect the same concept (virologic breakthrough). The Applicant's definition is: (a) In subjects with HBV DNA levels of ≥6 log_{10} c/mL at Baseline who subsequently achieved 2 consecutive HBV DNA values <5 log_{10} c/mL, and has (1) HBV DNA ≥5 log_{10} c/mL on 2 consecutive visits with no more than one subsequent value <5 log10 copies/mL or (2) HBV DNA ≥5 log_{10} c/mL at the last treatment visit OR (b) In subjects who never achieved 2 consecutive HBV DNA levels <5 log10 c/mL but achieved ≥2 log_{10} c/mL reduction from Baseline, and has (1) return of HBV DNA to within 1 log_{10} copies/mL of Baseline on two consecutive visits, with no more than one subsequent level >1 log_{10} c/mL below Baseline or (2) a single HBV DNA level within 1 log10 copies/mL of Baseline at the last treatment visit.

[29] The virologic analyses conducted by the Statistical Reviewer, Dr. Fraser Smith, used both an ITT population (instead of "as-treated" population) and the Applicant's definitions for the virologic endpoints. Dr. Smith's analyses were confirmatory of the Applicant's results.

MO Comments
Due to the hierarchical fixed testing hypothesis, the virologic response of subjects on LdT was deemed non-inferior to the response of subjects on LAM. Subjects on LdT, however, did achieve much greater HBV DNA suppression, particularly to PCR non-detectable levels, and much less virologic rebound (treatment failure) than subjects on LAM. There may be a virologic advantage of LdT relative to LAM, but this was not proven within the requirements of the statistical analysis agreed upon for this study. It is reassuring, however, that despite the more stringent virologic criteria for rebound (treatment failure) and HBV DNA reduction (<1000 copies/ml), LdT performed at least as well as LAM. While there are significant limitations to cross-study comparisons, and virologic response alone is not a reliable marker of disease improvement, it is interesting to note that LdT did not appear to perform as well as ETV (67% HBeAg-positives and 90% HBeAg-negatives achieved PCR non-detectable HBV DNA with COBAS Amplicor PCR assay).[30]

- In the paired sequence analysis of baseline and on-treatment samples, 75.7% (87/115) of subjects with evidence of virologic failure had genotypic changes in the HBV RT.
- Amino acid substitutions rtL80I/V, rtL180M, rtA181T, rtM204I, and rtL229W/V were associated with virologic failure to LdT therapy: these changes were detected in 48% (49/103) of the HBeAg-positive subjects and in 100% (12/12) of the HBeAg-negative subjects.
- 40% of subjects (46/115) had mutations at codon 204, rtM204: the rtM204I variants were detectable from the viruses of 37 subjects (80.4%) and the mixed variants, rtM204M/I or rtM204M/I/V were of 9 subjects (19.6%).
- Amino acid substitutions rtL80I/V, rtL180M, and rtL229W/V appeared tightly associated with the rtM204 mutation: all subjects that carry mutations at codons 80 (27 subjects), 180 (4 subjects), or 229 (6 subjects) were found to have the rtM204 mutation.
- In the subset of subjects with the rtM204 mutation, the mutation profile for LdT was similar to that for LAM with the exception of rtM204V mutation.
- The rtM204V mutation in conjunction with the rtL180M mutation was not detected.
- 13.9% of subjects (16/115) had mutations at codon 181, rtA181: the mixed variants, rtA181T/A, were detectable from the viruses of 8 subjects (50.0%), and the rtA181T and rtA181S variants were of 7 (43.8%) and of 1 (6.3%) subjects, respectively.
- No variants with rtA181V were detected.

There has been cross-resistance noted among HBV nucleoside analogues. The results of cell-based assays showed that LAM-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1000-fold reduced susceptibility to LdT. LdT kept its wild-type phenotypic activity (1.2-fold reduction) against rtM204V, associated with LAM-resistance. In cell culture, LdT is active against HBV encoding rtN236T, a substitution associated with the ADV resistance, however it is 3 to 5 times less active against rtA181V. Also, since ETV-associated resistance substitutions have emerged when LAM-resistant mutations at L180 and/or M204 are present, LdT is unlikely to retain efficacy among patients with ETV resistance because those patients will also have underlying LAM-resistant mutations

MO Comments
Based on in-vitro data, there is a slight possibility that LAM-resistant subjects with rtM204V mutation alone and ADV-resistant subjects with the rtN236T mutation might be susceptible to LdT. This has not been clinically verified. Also, it is unusual to find individuals with LAM resistance and the rtM204V mutation alone. Given LdT's non-inferior virologic (and overall treatment) response

[30] Tabel 3 in the Label for Baraclude™ (ETV) that was approved on March 29, 2005.

relative to LAM, the overlapping resistance profile with LAM and ADV, LdT's treatment niche remains unclear.

6.1.6 Efficacy Conclusions

The FDA Review Team concluded that in a well-conducted, multinational, pivotal Phase 3 study of subjects with compensated liver function, LdT was effective in the treatment of adults with chronic HBV infection and evidence of ongoing liver inflammation. The large Phase 3 study met the FDA criteria for an adequate and well-controlled study and had sufficient size to allow each of the two HBeAg subpopulations within the trial to serve, for analytical purposes, as a separate trial.

According to the statistical testing procedure pre-specified in the SAP, the superiority of LdT over LAM was also demonstrated in the HBeAg-positive subpopulation for Therapeutic Response, Histologic Response, Serum HBV DNA Reduction and Serum HBV DNA Undetectable. However since superiority for the same endpoints was not demonstrated in the HBeAg-negative subpopulation, the Division of Antiviral Products (DAVP) will require replication of the superiority

Non-inferiority of LdT to LAM was also demonstrated in the HBeAg-positive subpopulation for Virologic Response, HBeAg seroconversion and HBeAg Loss and in the HBeAg-negative subpopulation for Change in Ishak Fibrosis Score. Change in Ishak Fibrosis Score for LdT did not meet the pre-specified non-inferioritiy criterion for the HBeAg-positive subpopulation and the p-value for the difference between LdT and LAM was almost statistically significant in favor of LAM. This finding, although concerning, is tempered by the limitations of liver biopsy, and the more supportive findings of non-inferiority for other key efficacy endpoints, including histologic response, PCR non-detectable HBV DNA and Therapeutic Response.

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

There are limitations to the efficacy data presented in the LdT NDA. As noted above, the small number of blacks/African Americans enrolled in the clinical development program did not provide sufficient evidence to determine whether they respond differently to treatment with the drug and there were some possible treatment effect questions raised by the subgroup analsyses within the HBeAg-negative subpopulation. Some of these questions may also be related to the small numbers of female subjects.

There are no efficacy data submitted in the NDA regarding the efficacy of LdT in patients with decompensated liver disease due to chronic HBV infection, another important subgroup. Study NV-02B-011 is underway and is examining the safety and efficacy of LdT in this population. Finally, although the results of these studies support the non-inferiority of LdT treatment compared to LAM treatment by a variety of histologic, serologic, virologic, and composite endpoints measured at 52 weeks, there are no data comparing LdT to ADV or ETV for the treatment of

chronic HBV, although a comparison study with ADV is underway.[31] Key issues raised in this review that are not currently under investigation will be addressed in post-marketing commitments involving new or ongoing studies.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data for this NDA was provided in the form of final study reports, a summary of clinical safety, and electronic datasets containing tabulations of clinical adverse events and laboratory monitoring. Narrative summaries and case report forms were provided for all subjects who died, developed serious adverse events (SAEs), or discontinued study drug because of an adverse event (AE).

The review evaluated safety in the pivotal study, NV-02B-007 in detail. The Safety population for this study consisted of all subjects who presumptively received at least one dose of the study medication with at least one observation after Baseline. Subjects who received study treatment other than the one randomly assigned were to be analyzed according to treatment received. The Applicant reports that when they locked the database for the primary analysis, approximately 31% of subjects had completed the Week 68 study visit.

Tabulations of AEs, SAEs, deaths, study drug discontinuations, and laboratory abnormalities were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc). Some analyses, including Kaplan Meier time-to-onset curves, were made with the assistance of the Statistical Reviewer, Dr. Fraser Smith.

MO Comments
Throughout this Safety Review, AEs are presented as straight proportions rather than by duration of exposure. In addition, all FDA analyses of clinical adverse events were based on all visit information provided for the safety evaluable population at the time of the original NDA submission. All subject clinical adverse event data in the database at the time of database lock were analyzed for safety.

The supporting Phase 2b study, NV-02B-003, and its continuation study, NV-02B-010 were also reviewed; however since both studies had multiple arms and subjects on varying doses of LdT and/or LdT in combination with LAM, the data were not pooled with the pivotal study, NV-02B-007. FDA safety analysis was done separately for each study. If a potential safety signal was identified in the pivotal study, then the other studies were analyzed for confirmation.

[31] Study NV-02B-018 is a randomized, open label trial of LdT versus ADV in adults with HBeAg-Positive, compensated chronic HBV.

At the time of the 120-Day Safety Update, safety data was newly available for the NV-02B-015 study. This ongoing Phase 3 study is being conducted in China for the purpose of Chinese registration. Complete data up to Week 52 of the study were available by the 120-Day Safety Update cut-off date and since the study has an identical design to the pivotal trial, NV-02B-007, the Applicant pooled these data with Baseline to Week 52 data from NV-02B-007. The SAE, AE and death data from this pooled analysis were reviewed and will be described, as needed, for further supportive evidence of select observations in the pivotal trial.

The safety results of the other 25 trials, most of which are Phase 1 studies, were reviewed in less detail and the results of only significant findings or findings, which significantly strengthened or contradicted conclusions drawn in the pivotal trial, are presented below.
Please see Dr. Jennifer H. Zheng's review for an analysis of exposure-response for safety data.

For the interim analysis of the pivotal trial, the Applicant assessed the following safety endpoints:

- Death: total, attributable
- Serious Adverse Events: total, attributable
- Total Adverse Events, as coded by MedDRA
- Drug-Attributed Adverse Events
- Adverse Events considered to be at least possibly related to study drug by the investigator
- Discontinuation from the study, including Discontinuation from the study due to Adverse Events
- Discontinuation or modification of treatment due to Adverse Events
- Changes from Baseline in Clinical Lab Parameters
- Graded Laboratory Abnormalities
- Creatine Kinase (CK), Absolute Neutrophil Count (ANC), Platelet Counts
- ALT Flare phenomena
- Vital Sign Parameters

The Applicant adapted the "Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences" to report AEs and laboratory test abnormalities during the trial. The Applicant modified the severity gradings for AST, ALT, and alkaline phosphatase.

In the clinical adverse event listings datasets submitted with the NDA, 12.6% (173/1367) of study subjects had missing data for the adverse event date of onset (ONSETDT). In the majority of these cases, the month (ONSETMN) and year (ONSETYR) of onset and/or resolution were available, but the day (ONSETDY) was missing. Similarly, 10.9% (149/1367) of study subjects with available data for the month (RESOLVMN) and year (RESOLVYR) of clinical adverse event resolution had missing data for the day (RESOLVDY) of adverse event resolution.

MO Comments
The Medical Reviewer's approach to this missing data is described:

- *When ONSETDY was missing, but ONSETMN and ONSETYR were available, ONSETDY was assumed to be the first day of the month.*
- *Similarly, when RESOLVDY was missing, but RESOLVMN and RESOLVYR were available, RESOLVDY was assumed to be was assumed to be the 30th day of the month (or the 28th day for February).*

The Applicant evaluated clinical adverse events and laboratory abnormalities according to assigned treatment (LdT or LAM) and over 3 treatment periods:

On-Treatment Period

- Baseline to the date of last treatment + 7 days.[32]

Post-Treatment Period

- Safety-related follow-up period of the study, excluding the 7 days after the date of last treatment for subjects who discontinued from the study or who elected not to enter the follow-up study, NV-02B-022. Subjects who joined the follow-up study did not to have NV-02B-007 post-treatment data.

Off-Treatment Period

- Applicable only for subjects who discontinued treatment due to efficacy during the study. For subjects who did not experience post-treatment relapse, the off-treatment period is defined as 8 days after the date of last treatment through the subject's follow-up period. If the subject does not have a follow-up visit, the date of study discontinuation was used. For subjects who experienced a post-treatment relapse, the off-treatment period was 8 days after post-treatment discontinuation through the subject's date of restarting

MO Comments

The Applicant designed their analyses to capture adverse events as on-treatment for 11.2 half-lives (7 days) after the subject discontinued study drug. Throughout the analysis of clinical adverse events, this Medical Reviewer analyzed clinical adverse events according to assigned treatment (LdT or LAM) and over 2 study periods (on-treatment and off-treatment[33]). A clinical adverse event was considered on-treatment if it occurred while on study drug or within 30 days (48 half-lives) of study drug discontinuation. Although few subjects discontinued study drug during NV-02B-007, the difference in the definition of on-treatment between this Medical Reviewer and the Applicant, contributed to slight differences between the numerical results generated in the clinical AE analyses.

All subjects who received at least one dose of blinded study medication in the pivotal trials were included in the safety analyses. This included data on 1367 nucleoside-naïve subjects (680 LdT subjects, 687 LAM subjects). The review included assessment of proportions of subjects who experienced AEs and SAEs according to severity, relationship to blinded study drug, and action required to manage the event (e.g. discontinuation of study drug).

Summary results of the analysis will be presented below. Minor differences between the Applicant's results and the FDA's results can be attributed to the differences in "on-treatment" definitions, as described above, categorizing of adverse events, and methods for conducting the analyses and do not significantly alter the final conclusions.

In general, the safety profile of LdT was similar to that of LAM in the pivotal and supporting studies. AEs were reported frequently, although there were few differences in the pattern of AEs reported by LdT-treated subjects compared to LAM-treated subjects. The most notable differences were in the increased risk of CK elevations among subjects on LdT and ALT elevations among subjects on LAM.

The number of subjects who developed SAEs while on study drug (death, hospitalization, cancer, congenital anomaly, life-threatening condition, or other medically significant event) was small.

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[32] For subjects who discontinued treatment due to efficacy, if the subject resumed treatment due to post - treatment relapse, the On-Treatment period also included the time from restarting blinded medication to 7 days after the subject's date of last treatment.

[33] Unlike the Applicant, during the analysis of clinical adverse events, the Medical Reviewer defined off-treatment clinical adverse events as all those AEs occurring 30 days or more after study drug discontinuation.

Similarly, the number of subjects discontinuing their assigned study drug because of an AE or SAE was low, 0.6 % (4/680) for LdT-treated subjects and 1.0 % (7/687) for LAM-treated subjects. Table 7.1A summarizes the prevalence of common AEs and SAEs. More detailed description of the integrated safety review will be provided in the sections to follow.

Table 7.1A: NV-02B-007: Proportions of Subjects Reporting On-Treatment Adverse Events or Serious Adverse Events

	LdT (n=680)	**LAM (n=687)**
Subjects reporting any AE	513 (75.6%)	491 (71.5%)
Subjects with AE possibly or probably related to drug [a]	167 (24.6%)	141 (20.5%)
Subjects with Grade 3 or 4 AE	35 (5.2%)	47 (6.8%)
Subjects with Grade 3 or 4 and related AE	7(1.0%)	10 (1.5%)
Subjects reporting any SAE	28 (4.1%)	40 (5.8%)
Subjects with SAE possibly or probably related to drug [b]	3 (0.4%)	1 (0.2%)
Subjects discontinuing study drug due to any AE or SAE	5 (0.7%)	6 (0.9%)

Source: Medical Officer's review of the electronic listings datasets, AE and DRUGDISP for NV-02B-007
[a,b] AE or SAE relatedness to study drug based on Investigator assessment

7.1.1 Deaths

A total of 13 deaths have occurred during treatment with study drugs during all of the LdT studies submitted in the original NDA and 120-Day Safety Update (See Table 7.1.1A). There had been only one subject death in the pivotal trial, NV-02B-007. Subject # 118-013, a LAM recipient, died in a motor vehicle accident; this death was not attributed to study drug. No subjects died during the NV-02B-003 or NV-02B-010 studies. Only one death was considered possibly or reasonably related to the study drug by the Applicant, LAM-treated subject in NV-02B-015, Subject # 008-022.

Table 7.1.1A: Cumulative Death Summary in LdT Clinical Trials (through 1/31/06)

Study Number NV-02B-	**Subject ID**	**Study Drug**	**Onset Study Day**	**Cause of Death**	**Relatedness to Study Drug**
007	118-013	LAM	237	Traffic Accident	Not possibly or reasonably related
015	010-001	LdT	128	Murder	Not possibly or reasonably related
015	008-022	LAM	469	Hepatic Failure	Possibly or reasonably related
011	041-006	Blinded	419	Cerebral hemorrhage due to hypertension	Not possibly or reasonably related

011	024-009	Blinded	122	Sepsis	Not possibly or reasonably related
011	018-007	Blinded	126	Hepatic encephalopathy with severe UGIB	Not possibly or reasonably related
011	020-002	Blinded	78	Subacute liver failure	Not possibly or reasonably related
011	029-006	Blinded	72	Septic Shock	Not possibly or reasonably related
011	029-007	Blinded	12	Spontaneous bacterial peritonitis	Not possibly or reasonably related
011	037-001	Screening	NA	Portal vein thrombosis	Not possibly or reasonably related
011	041-007	Blinded	75	Hepatic encephaolpathy	Not possibly or reasonably related
019	018-017	Screening	NA	Acute tonsillitis with ARDS	Not possibly or reasonably related
006	Not applicable	Screening	NA	Urosepsis	Not possibly or reasonably related

Source: Medical Officer's review of electronic AE datasets submitted with the 120-DaySafety Update for NV-02B-007 and NV-02B-015; Clinical Summary Document for 120-Day Safety Update; Post-Text Table 9.3.1.5 for the 120-Day Safety Report, 27-CLIN-SUM APP-0010.

MO Comments
Based on review of the narrative summaries and CRFs provided, the reviewing Medical Officer agrees with the Applicant's assessment of causality for the deaths in the LdT clinical development program. Overall, the number of deaths has been relatively low in the LdT development program. There does not seem to be a relationship between study drug dose, duration, or other factors and the report of deaths among subjects in the safety population.

7.1.2 Other Serious Adverse Events

The number of subjects in the pivotal trial, NV-02B-007 who developed SAEs while on study was relatively small. In the pivotal study, there were 79 on-treatment Serious Adverse Events among 63 (4.6%) subjects (24 LdT; 39 LAM), 29 of whom were HBeAg-negative and 34 of whom were HBeAg-positive. SAEs reported in 2 or more subjects on treatment are summarized in Table 7.1.2A. Among the subjects reporting SAEs, only 1 LAM subject (urticaria) compared to 3 LdT subjects (2 with increased CPK and 1 with myopathy) had an SAE that was considered possibly, probably, or certainly related to study drug, as shown in Table 7.1.2B. There were six SAEs, four in the LdT arm and two in the LAM treatment arm, occurring off-treatment. Based on review of the narrative summaries and CRFs provided, the reviewing Medical Officer agrees with the Applicant's assessments of causality for all except the following SAEs in 2 subjects on LdT: pyrexia (003-205); pyrexia (019-017).

Table 7.1.2A: NV-02B-007: Serious On-Treatment AEs Occurring in ≥ 2 Subjects

Adverse Event N (%)	**LdT (n=680)**	**LAM (n=687)**

Abdominal Pain	0	2
Ankle Fracture	1	1
Appendicitis	0	2
CPK increased	2	0
Cellulitis	1	1
Hepatic Neoplasm Malignant	0	2
Hepatitis B exacerbation	0	2
Pneumonia	2	0
Pyrexia	2	0
Renal Colic	0	2
Wound Infection	0	2

Source: Medical Officers' review of the AE and DRUGDISP listings datasets for NV-02B-007

In NV-02B-007, there seemed to be a clustering of SAEs in the Muscoloskeletal and Connective Tissue Disorders SOC, among LdT recipients. One LdT-treated subject each experienced an on-treatment SAE of musculoskeletal chest pain (Subject # 061-035) and myopathy (Subject # 012-001)). Review of data from NV-02B-015 in the 120-Day Update revealed that an additional telbivudine-treated subject (Subject # 010-023) had developed an SAE of polymyositis. These cases are discussed in further detail below in Section 7.1.3.3, Other Significant Adverse Events.

MO Comments
The clustering of the SAEs of musculoskeletal chest pain, myopathy and polymyositis, all in the Musculoskeletal and Connective Tissue Disorders SOC, among LdT recipients suggests an association between study drug and infrequent serious adverse events in this SOC. Given the severity of these adverse events, the association between LdT and SAEs in the Musculoskeletal and Connective Tissue Disorders SOC warrants more careful evaluation (see Section 7.1.3.3, Other Significant Adverse Events).

Table 7.1.2B: NV-02B-007: Subjects Reporting On-Treatment Serious AEs

	Serious Adverse Events (SAEs)		
	LdT (n=680)	**LAM (n=687)**	**Totals (n=1367)**
Number of Subjects	**24 (3.5%)**	**39 (5.7%)**	**63 (4.6%)**
Number of SAEs	31	48	79
SAE possibly, probably or certainly related to study drug	3	1	4
• Grade 1 and 2, possibly, probably, or certainly related to study drug	2	1	3
• Grade 1 and 2, unrelated	24	26	50

to study drug			
• Grade 3 and 4, possibly, probably, or certainly related to study drug	1	0	1
• Grade 3 and 4, unrelated to study drug	4	21	25

Source: Medical Officers' review of the electronic listings datasets AE, DRUGDISP for NV-02B-007

In the supporting Phase 2b study, NV-02B-003, there were 2 subjects with serious AEs, both of whom were on LdT. One subject developed a malignant mediastinal neoplasm (Grade 3) while on LdT 600mg and another developed papillary thyroid cancer (Grade 2) while on LdT 600mg. Both events were considered unrelated to the study medication. In NV-02B-010, the follow-on study of NV-02B-003, there were four subjects with serious AEs. Two of these subjects were on LdT 600mg (jaw fracture and nasopharyngeal carcinoma), one was on LAM (hepatitis), and another was on a combination of LdT 600mg and LAM 100mg (abdominal mass and melena due to metastatic thymic cancer). According to the Applicant, none of these SAEs was related to the study medication, except for the acute exacerbation of hepatitis B in one subject on LAM. Another subject on LdT 600mg had a hepatitis flare off treatment, after discontinuing study drug for efficacy, but this was deemed unrelated to the study drug. All of these SAEs resolved without residual effects, except for nasopharyngeal carcinoma that developed in one subject on LdT 600mg. For NV-02B-010, three additional SAEs were reported after the cutoff date, only one of which (hepatic flare due to drug resistant mutants), has been attributable to the study drug.

MO Comments
The reviewing Medical Officer agrees with the Applicant's assertion that the SAEs in NV-02B-003 and its follow-on study NV-02B-010 were unrelated to study drug.

The pooled AE datasets for studies NV-02B-007 (Wk 76 data) and NV-02B-015 (Wk 52 data,) provided in the 120-Day Safety Update, did not reveal differences in the nature or frequency of SAEs or types of SOCs affected when compared to the original NDA submission. Of note, there was one additional LdT-associated case of pyrexia, and one additional LdT-associated case of coronary artery disease (089-002) in the pooled AE dataset for NV-02B-007 and NV-02B-015, raising the total numbers of subjects in these AE categories to 3, 2, and 2 respectively. None of these AEs were thought to be possibly or reasonably associated with the study drug, based on review of the narratives. Two additional NV-02B-007 subjects (016-012 and 118-008) on LdT were found to have an SAE of HBV flare, between Week 60 and 68 for 016-012 and Week 100 for 118-008. While the flare for subject 016-012 was considered possibly or reasonably associated with the study drug, the causality of the HBV flare for subject 118-008 remains unknown.

MO Comments
Based on review of the narratives, the Medical Reviewer agrees with the Applicant that the SAEs of coronary artery disease are not reasonably or possibly related to the study drug. Both were male subjects in their 50s withs concomitant risk factors for coronary artery disease. This Medical Reviewer does not agree with the Applicant's attribution of causality for the SAEs of pyrexia. Also, there were no SAEs of hepatic flare among subjects on LdT until the second year of treatment. It remains unclear whether or not the proportion of LdT subjects with hepatic flares will increase during the second year of therapy, possibly limiting its current advantage over LAM in the development of hepatic flares.

Among the ongoing, blinded studies, there have been numerous SAEs in NV-02B-011, a study whose subjects have chronic hepatitis B with decompensated liver disease. In this study, there have been 42 SAEs among 27 subjects, 8 of which occurred prior to receiving study medication. None of these SAEs has been attributed to the study drug.

MO Comments
A higher rate of adverse events is expected in this sicker population of decompensated subjects.

At the time of NDA submission, three SAEs had been reported in the still-blinded studies, NV-02B-018 and NV-02B-019, respectively, none of which have been attributed to the study drug.

Two SAEs have been reported in two subjects in the clinical pharmacology studies NV-02B-006 and NV-02B-024. The subject in NV-02B-006 was randomized to study drug, but never treated due to the SAE of urosepsis and his subsequent death (see Table 7.1.1A). The subject with an SAE in NV-02B-024 was on placebo.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The proportions of subjects discontinuing study drug in the pivotal, Phase 3 study, NV-02B-007, and their reasons for study drug discontinuation are shown in Table 7.1.3.1A below. The study designs for the supporting Phase 2b study, NV-02B-003, and its follow-on study, NV-02B-010 are dissimilar from NV-02B-007, making comparison more difficult. Hence, the subject disposition data for the trials are examined separately.

In NV-02B-007, 1376 subjects were randomized to either LdT or LAM within 24 hours of the Baseline visit. This exceeds the 1200 planned subjects because subjects who were in Screening when the target accrual was reached were allowed to enter the study. Six subjects did not return for the Baseline visit and these subjects were not captured in the clinical database. In addition, three subjects did not have post-Baseline observations. These nine subjects were excluded from all analyses, resulting in an ITT population of 1367 subjects.

Table 7.1.3.1A: NV-02B-007: Subject Disposition by treatment group for the first year of dosing

Disposition of Subjects	**LdT** (n=680)	**LAM** (n=687)	**Total Subjects** (n=1367)
Total Treated	**680**	**687**	**1367**
Subjects discontinued from Study	**43**	**45**	**90**
• Adverse Event [a, b, c, d]	4	7	14
• Death	0	1	1
• Non-Compliance [e]	4	3	7
• Pregnancy	1	2	3
• Subject, Investigator, Applicant-Initiated Request	13	20	33
• Clinical Disease Progression	0	4	3
• Lack of Efficacy after week 24 [f]	0	3	3

• Achieved Efficacy Criteria[g, h]	21	5	26
Subjects continued in study	**637**	**642**	**1279**

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

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

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

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

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

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

[f] Per the study protocol, the subjects who met either or the two following criteria at week 24 or subsequently were discontinued from the study for "lack of efficacy at Week 24" and categorized as treatment failures in the analyses of efficacy : (1) At Week 24 or thereafter, ALT increased to 10 x ULN (and at least 2 x Baseline) on two or more visits over a period of at least 7 days; AND serum HBV DNA was ≥ 6 log10 copies/mL OR the serum HBV DNA pattern met either of the Applicant's virologic breakthrough definitions OR (2) Over 16 weeks of the study, at any time after Week 24, ALT was persistently elevated to levels ≥ 2 x ULN (and ≥ Baseline ALT) AND serum HBV DNA is ≥ 6 $\log_{10}$ copies/mL OR serum HBV DNA pattern met either of the Applicant's virologic breakthrough definitions (described in Section 6.1.5, Clinical Microbiology).

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

[h] Per the study protocol, treatment discontinuation (WITHOUT study discontinuation) for "Efficacy" was deemed appropriate for some subjects at Week 52 or subsequently, as follows: (1) For subjects who were HBeAg-positive at entry, discontinuation of study drug treatment was allowed for subjects who have completed at least 52 weeks of study drug treatment, who exhibit Virologic Response (HBV < 5 $\log_{10}$ copies/mL) and who have exhibited HBeAg loss for at least 24 weeks; (2) For subjects who were HBeAg-negative at entry, treatment discontinuation was deemed appropriate only for subjects who have achieved HBsAg loss at Week 52 or subsequently, documented on two successive study visits.

Overall, however, a greater proportion of subjects on LAM (2.0%) discontinued study drug due to an adverse event, lack of efficacy, or clinical disease progression than subjects on LdT (0.6%).

MO Comments

There are slight differences between the subject disposition described by the Applicant and the Medical Reviewer's results listed above in Table 7.1.3.1 A. This Medical Reviewer recoded the reason for discontinuation for some of the subjects as per the explanation provided in the notes underneath Table 7.1.3.1 A. Also, additional subjects with study drug discontinuations due to adverse events were found in the adverse event dataset that were not included in the Applicant's overall tabulation of study drug discontinuations due to adverse events. Overall, fewer LdT subjects than LAM subjects discontinued study due to adverse events or lack of efficacy and more LdT subjects discontinued study drug due to efficacy associated with the treatment.

The analyses described in the above section are based on the data available at the time of database lock. The NV-02B-007 study is ongoing and, as noted above in Table 7.1.3.1A, the majority of subjects have continued into the second year of dosing.

7.1.3.2 Adverse events associated with dropouts

In NV-02B-007, at the time of database lock for the original NDA submission, the total number of subjects discontinuing their assigned study drug because of an AE or SAE was low, 4/680 (0.6 %) of LdT-treated subjects and 7/687 (1.0 %) of LAM-treated subjects. The rate of study drug discontinuation due to AEs was slightly higher in the LAM treatment group. The most common AEs resulting in study drug discontinuation for LAM subjects were hepatitis related, including hepatic encephalopathy, exacerbation of hepatitis and increased ALT/AST (0 LdT, 4 LAM). Discontinuations due to AEs, based on all data provided at the time of database lock, among subjects in NV-02B-007, are tabulated in Table 7.1.3.2A.

Table 7.1.3.2A: NV-02B-007: Subjects Reporting Adverse Events Resulting in Study Drug Discontinuation in the Safety Evaluable Population

Subject ID Number	Treatment	Age/Sex/Race	AE Resulting in Discontinuation	Toxicity Grade	Relationship to Study Drug	Days on SD at AE Onset[a]	Total Days on SD
005-007	LdT	43/M/Asian	Nausea/Loose Stool	1	RPR[b]	389	446
025-008	LdT	42/M/African-American	Elevated CK	2	RPR	274	309
071-001	LdT	59/M/Caucasian	Congestive Heart Failure	2 (SAE)	NRPR[c]	563	590
131-002	LdT	21/M/Middle Eastern/Indian	Lethargy	1	RPR	6[d]	34
012-015	LAM	59/M/Asian	Multiple Myeloma	4(SAE)	NRPR	153	154
008-079	LAM	52/F/Asian	Urticarial Rash	4(SAE)	RPR	3	4
030-001	LAM	32/M/Caucasian	Elevated AST/ALT	4	RPR	374[e]	374
034-002	LAM	56/F/Caucasian	Nasal and Oral Mucosal Dehydration	2	RPR	168	204
057-065	LAM	37/M/Other	Hepatic Encephalopathy	4(SAE)	NRPR	323	323
095-002	LAM	30/M/Asian	ALT Elevation	2(SAE)	NRPR	57	85
008-036	LAM	60/F/Asian	ALT Elev/Viral Breatkthrough	1	NRPR	484	494

Source: Medical Officer's review of the listings datasets for NV-02B-007: CKELEV, AE, DRUGDISP, STUDYSUM, DISC, the analysis dataset, A_AE for NV-02B-007, the AE listings dataset for NV-02B-007 submitted with the 120-Day Safety Update and the CRF for Subject# 057-123. Subjects who had not yet received study drug at the time of their adverse event were excluded.

[a] Based on Study Day of Last Dose of Study Drug
[b] RPR = Reasonably or Possibly Related
[c] NRPR = Not Reasonably or Possibly Related
[d] This adverse event resolved 31 days after study drug discontinuation.
[e] This AE occurred on day 394, 20 days after last dose

MO Comments

The assessment of whether these events were related to study drug was based on the judgment of the individual investigators. These judgments may have been somewhat subjective since the side effect profile of LdT was not fully characterized at the time of the studies. However, most investigators had reasonable experience in the use of LAM for treatment of HBV and extensive

experience with the complications of the underlying disease. Although, study drug use was blinded, it was not placebo-controlled, likely introducing some bias in assigning a relationship between study drug and a given AE.

This Medical Reviewer also agrees with the causality assessment of the study investigator (NRPR) for the SAE of Congestive Heart Failure that led to discontinuation of study drug (LdT) in Subject # 071-001. Review of the narrative provided for this subject revealed a pre-existing history of coronary artery disease. Stenosis found on the coronary angiogram performed at the time of the SAE of congestive heart failure.

An additional NV-02B-007 subject on LdT (#012-001) that was described in the original NDA submission was discontinued from study drug shortly after the onset of an adverse event of elevated CK & drug- induced myopathy. The subject coincidentally met discontinuation criteria for efficacy and the reason provided by the Applicant for study drug discontinuation was efficacy, not an adverse event. This case is discussed in further detail in Section 7.1.3.1, Other Significant Adverse Events.

MO Comments
Subject # 012-001 met criteria for study drug discontinuation due to efficacy; however, the concurrent adverse event would have warranted study drug discontinuation if this subject had not met discontinuation criteria for efficacy. While this subject has not been included as a discontinuation due to an adverse event in Table 7.1.3.A, this Medical Reviewer recognizes that this type of adverse event raise important safety concerns for LdT and should result in study drug discontinuation.

Overall, 28 subjects (LdT: 14; LAM: 14 interrupted) and 11 subjects (LdT: 4; LAM: 7) discontinued study drug because of an adverse event. Among the study drug interruptions and discontinuations, the most common System Organ Classes (SOCs) were Gastrointestinal and Investigations. Adverse events within the Investigations SOC included Blood CPK increased, HBV DNA Increased and other findings shown in Table 7.1.3.2 B beow.

Based on review of the combined data for NV-02B-007 and NV-02B-015 submitted with the 120-Day Safety Update, Table 7.1.3.2.B is presented below.

Table 7.1.3.2B: All On-Treatment Adverse Events leading to Study Drug Discontinuation to Week 104-Pooled Studies NV-02B-007 and NV-02B-015 [a]

Disposition of Subjects	**LdT** (n=847)	**LAM** (n=852)
Subjects Reporting an AE leading to dose interruption or drug discontinuation, n (%)	**13 (1.5)**	**12 (1.4)**
System Organ Class (n, %) /Preferred Term		
Cardiac Disorders	**1 (0.1)**	**0**
• Cardiac failure, congestive	1	0
Gastrointestinal Disorders	**2(0.2)**	**1(0.1)**

• Nausea	2	0
• Abdominal Distention	1	0
• Loose Stools	1	0
• Vomiting	1	0
General Disorders & Administration Site Conditions	**2(0.2)**	**1(0.1)**
• Fatigue	1	0
• Influenza-Like Illness	1	0
• Mucous membrane disorder	0	1
Hepatobiliary Disorders	**1(0.1)**	**0**
• Hepatic Failure	1	0
Infections and Infestations	**1(0.1)**	**5(0.6)**
• Hepatitis B	1	5
Investigations	**5(0.6)**	**2(0.2)**
• Blood CPK Increased	3	0
• Blood CPK MB Increased	1	0
• HBV DNA Increased	1	0
• Weight Decreased	1	0
• ALT Increased	0	2
• AST Increased	0	1
Musculoskeletal & Connective Tissue Disorders	**3 (0.4)**	**0**
• Myalgia	1	0
• Myopathy	1	0
• Myositis	1	0
• Pain in extremity (aching pain in legs)	1	0
Neoplasms benign, malignant and unspecified	**0**	**1(0.1)**
• Multiple myeloma	0	1
Nervous System Disorders	**0**	**1(0.1)**
• Hepatic Encephalopathy	0	1
Skin & Subcutaneous Tissue Disorders	**0**	**1(0.1)**
• Urticaria	0	1
Social Circumstances	**1(0.1)**	**0**
• Murder	1	0

Source: Table 4-22 from 120-Day Safety Update Summary Document, released on 4/21/06.
[a] In this table, provided by the Applicant, "on-treatment" refers to AEs that occurred while on study drug or within 7 days of the last dose of study drug.

The SOCs of Investigations and Musculoskeletal and Connective Tissue Disorders were most often reported as the reason for discontinuation in LdT-treated subjects from the pooled dataset. The most common reason for discontinuation among those subjects on LdT who discontinued in the Investigations SOC was CK elevation. All three subjects who discontinued had eventual resolution of their CK elevations. Of the three subjects in the Musculoskeletal and Connective Tissue Disorders SOC who discontinued study drug, one subject (007-057-123) experienced Grade 1 myalgia, Grade 1 myositis and decreased weight, while another subject discontinued for pain in the extremity. A third subject (007-054-031,) described in the 120-Day Safety Update, experienced a Grade 2 myopathy after NDA cutoff and discontinued treatment with LdT during the second year of the NV-02B-007 study. The occurrence of myopathy in this case was temporally associated with CK elevations. Study drug was discontinued due to the myopathy, and the subject discontinued from the study one month later. These subjects will be discussed in more detail below in Section 7.1.3.3, Other Significant Adverse Events. Of note, there were six subjects in the combined dataset

for the NV-02B-007 and NV-02B-015 studies, all of whom were on LdT, with AEs in the Musculoskeletal and Connective Tissue Disorders SOC that interrupted treatment due to these AEs.

Although no subjects on LAM had discontinued study drug due to a CK elevation or muscle-related adverse event at the time of the original NDA submission or the 120-Day Safety Update, the Applicant's review of their AE database in August, 2006 revealed that two additional subjects on LdT (007-122-054, 015-006-004) and one additional subject on LAM (007-079-004) had discontinued study drug due to an elevation in CK and/or muscle-related adverse events. These and other CK-related adverse events resulting in study drug discontinuation among LdT subjects and LAM subject are discussed in more detail below in Creatine Kinase Elevations: Drug-Associated Myopathy in Section 7.1.3.3, Other Significant Adverse Events.

MO Comments
There is overlap between the subjects described in Table 7.1.2.3A and B. While there were similar proportions of subjects discontinuing or interrupting study drug due to an AE between the study drug and comparator arms, more subjects discontinued due to musculoskeletal and connective tissue disorders and/or CK elevations in the LdT arm than the LAM arm (Table 4-22, 120-Day Safety Update). Although the proportion of subjects discontinuing for each Preferred Term is small, there is an indication that the musculokeletal and CK-related adverse event terms leading to study discontinuation are LdT-related.

In the NV-02B-003 and its rollover study, NV-02B-010, a total of 11 subjects reported AEs leading to discontinuation, with Investigations, again being the most commonly reported SOC in all treatment groups. As in NV-02B-007 and NV-02B-015, elevations of AST, ALT were more common in LAM-treated subjects than LdT-treated subjects, but the numbers of subjects were extremely small in the LAM treatment group. No subjects discontinued due to an elevated CK or musculoskeletal or connective tissue disorder in these Phase 2b studies. CK elevations were not measured in the remaining Phase 1 and 2 LdT studies.

7.1.3.3 Other significant adverse events

Some adverse events were evaluated and reported in more detail because of special significance for the review of nucleoside analogues, including LdT, and/or the presentation of a safety signal. Among these events were CK elevations, drug-associated myopathies, acute exacerbations of hepatitis or ALT flares and other significant hepatic AEs, amylase and lipase elevations, and lactic acidosis. Although several of these adverse events may be linked to drug-associated mitochondrial toxicity, there was no appreciable evidence of mitochondrial toxicity in preclinical testing of LdT. Please see Section 6.1.5, Clinical Microbiology.

Creatine Kinase Elevations
In preclinical toxicity studies for LdT, creatine kinase levels were not routinely assessed. Muscle-related toxicity was also not observed in the preclinical toxicology studies. CK levels were previously known to fluctuate in the 'normal' population without evidence of muscle disease, and elevated levels were observed to fluctuate in placebo-treated hepatitis B subjects in the LAM and ADV Phase 3 trials. As a result, the clinical protocols of the LdT development program did not require normal CK levels at study entry. Elevated CK levels were abnormal in a proportion of subjects at Screening and Baseline in the LdT clinical trials. In July 2003, the Division noted a trend in the number of LdT subjects in the NV-02B-003 study that had increased Grade 1-4 creatine

kinase (CK) levels, resulting in the addition of a separate analysis for CK levels to the Statistical Analysis Plan for NV-02B-007. In NV-02B- 007, variability in baseline CK was noted in both HBeAg subpopulations ranging from 25 IU/L to 3438 IU/L in HBeAg-positive and 36 IU/L to 964 IU/L in the HBeAg-negative populations. A slightly higher proportion of LdT-treated subjects in the HBeAg-negative population entered NV-02B-007 with graded pretreatment CK elevations.

Table 7.1.3.3 A shows the proportion of subjects who developed new-onset[34] Grade 1-4 CK elevations, stratified by their baseline toxicity grade. The percentage of subjects with new-onset Grade 1-4 CK elevations was significantly higher in LdT subjects; 488/680 (71.8 %) compared to 285/687 (41.5%) of LAM subjects ($p<0.001$ using Fisher's Exact test).[35] When broken down by grade, the percentage of subjects with new grade 1-2 CK elevations was also significantly higher in LdT subjects; 427/680 (63%) of LdT subjects had new grade 1-2 CK elevations compared to only 263/687 (38%) of LAM subjects ($p<0.001$ using Fisher's Exact test).[36] The difference was even starker for Grade 3 and Grade 4 abnormalities, with 61 (9.0%) subjects on LdT developing Grade 3-4 elevations and only 22 (3.2%) subjects on LAM developing Grade 3-4 CK elevations. Fractionation of the available sera from subjects with Grade 3-4 CK elevations (sera from 61 subjects total) was performed to determine the isoenzyme subtypes. The results showed 99-100% CK-MM. In these cases, there was no evidence of myocardial –band (MB) to the observed CK elevations. The vast majority of subjects with pretreatment CK elevations, however, did not experience Grade 3 or 4 CK elevations on study.

Table 7.1.3.3 A: NV-02B-007: Summary of New-Onset, On-Treatment CK Elevations by Baseline Toxicity Grade during the First Year of Treatment

Baseline CK Toxicity Grade	**Maximum CK Toxicity Grade**				
LdT (n=680) N (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1-4**
Normal	280 (41.2)	108 (15.9)	22 (3.2)	17 (2.5)	427(62.8)
Grade 1	0	39 (5.7)	8 (1.2)	10 (1.5)	57 (8.4)
Grade 2	0	3 (0.4)	0	4(0.6)	7(1.0)
Grade 3	0	0	0	0	0
Grade 4	1	0	0	0	0
	280(41.2)	147 (21.6)	30(4.4)	31(4.6)	**488 (71.8)**

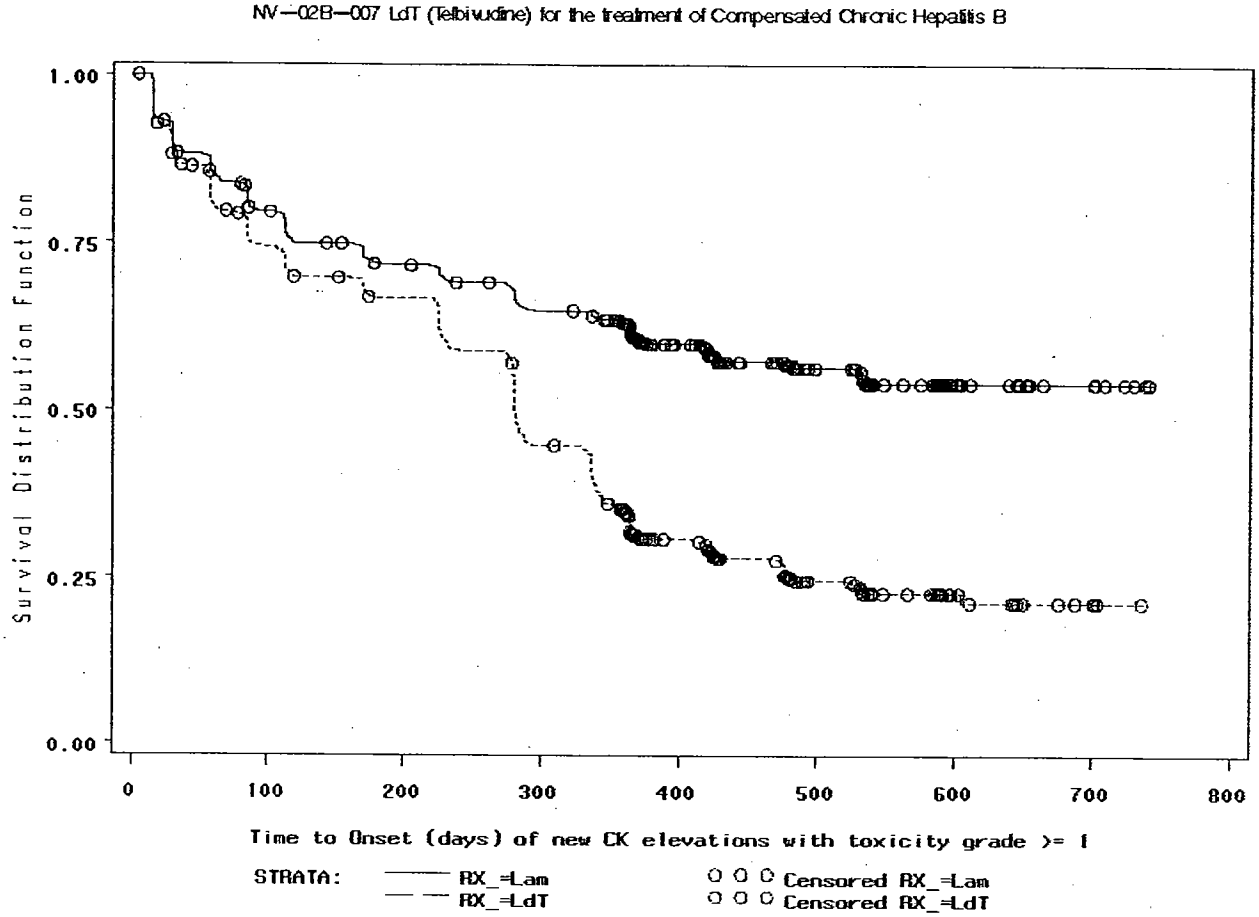
[34] An elevation was considered to be "new-onset" if the on-treatment CK toxicity grade was greater than the baseline toxicity grade.
[35] p-value based on Statistical Reviewer, Dr. Fraser Smith's, analysis.
[36] p-value based on Statistical Reviewer, Dr. Fraser Smith's, analysis.

LAM (n=687)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1-4
Normal	215 (31.3)	27 (3.9)	2 (0.3)	9 (1.3)	253 (36.8)
Grade 1	0	21 (3.1)	4 (0.6)	2 (0.3)	27 (3.9)
Grade 2	0	0	1 (0.1)	4 (0.6)	5 (0.7)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
	215 (31.3)	48 (7.0)	7 (1.0)	15 (2.2)	**285 (41.5)**

Source: Medical Officer Review of electronic analysis dataset for NV-02B-007, LABBYPT3 in combination with Statistical Reviewer analysis

Relatively similar proportions of subjects developed Grade 1-4 CK elevations during the first 6 months of study treatment. As shown below in Figure 7.1.3.3A, the Kaplan-Meier plot of time to onset of new-onset Grade 1-4 CK elevations, CK levels were similar between the treatment arms until the incidence of CK elevations appeared to gradually increase among LdT subjects relative to LAM subjects after approximately 100-150 days on study drug. The Applicant's analysis suggests that the higher incidence of CK elevations among LdT recipients started after Week 24. Both the Applicant analysis and the FDA analysis reveal that the higher incidence of CK elevations among LdT subjects relative to LAM subjects continued to grow until it eventually reached a plateau after about one year of therapy.

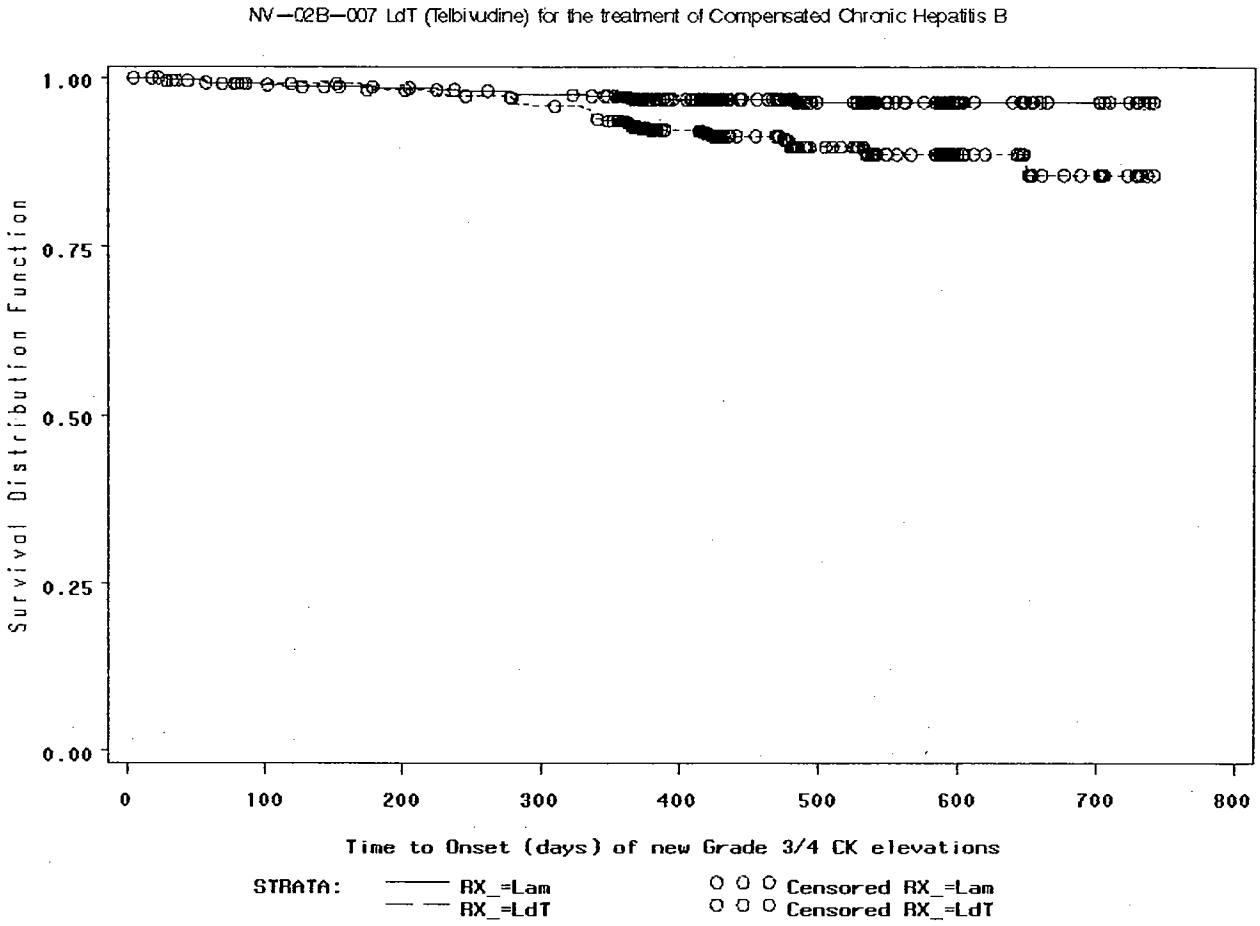
Figure 7.1.3.3A: NV-02B-007: Time-to-Onset (days) of New-Onset CK Elevations (Grade 1-4)



Source: Kaplan-Meier plots of time-to-onset of Grade 1-4 CK elevations generated by Statistical Reviewer, Dr. Fraser Smith. Grade 1-2 CK elevations are only counted for subjects who did not have Grade 3-4 CK elevations.

As shown in Figure 7.1.3.3B, the Kaplan-Meier plot of time to onset of new-onset grade 3-4 CK elevations, CK levels were similar between the treatment arms until fewer LAM-treated subjects than LdT-treated subjects appeared to develop CK elevations around Study Day 300.

Figure 7.1.3.3B: NV-02B-007: Time-to-Onset (days) of New-Onset CK Elevations (Grade 3-4)



Source: Kaplan-Meier plots of time-to-onset of Grade 3-4 CK elevations generated by Statistical Reviewer, Dr. Fraser Smith. Grade 1-2 CK elevations are only counted for subjects who did not have Grade 3-4 CK elevations.

MO Comments

The Kaplan-Meier plots of time-to-onset reveal a slightly earlier time to onset than the Applicant for the higher incidence of CK elevations among LdT recipients relative to LAM recipients. This discrepancy may be due to differences in analytical approaches (e.g. Kaplan-Meier plots versus cross tabulations over 6 month time periods) and the possibly large window of time during which a Week 24 study visit may occur, thereby limiting the utility of study days for comparison. The overall trends in the incidence and time to onset of new-onset Grade 1-4 CK elevations between the treatment arms found by this Medical Reviewer and the Applicant are similar.

The greater incidence of Grade 3-4 CK elevations found among LdT-treated subjects relative to LAM-treated subjects in the second year of treatment is more difficult to interpret, however, due to the very small numbers of subjects in the safety database with data past Week 52. Among those subjects, only a small minority experienced Grade 3-4 CK elevations, therefore even small changes in the study enrollment (e.g. study drug discontinuation among LAM subjects) could result in a relatively large disparity in the frequency of CK elevations between the treatment arms.

Although the Phase 2b supporting study, NV-02B-003, was relatively small and underpowered, data were generated regarding the effect of LdT dose (e.g. comparison of 400 mg versus 600mg

LdT) and co-administration of LAM on CK levels. The Applicant reports that median CK levels tended to increase over time in all groups, with more pronounced increases after the first 24 weeks of treatment, especially for subjects receiving LdT-containing regimens. At the end of the 52-week primary treatment period, the median CK level was 123 IU/L for the LAM monotherapy cohort and ranged from 168 IU/L to 224 IU/L for the four LdT-containing treatment regimens.[37] The median values for the two LdT monotherapy cohorts at Week 52 were still within the central laboratory's normal range for CK (males 24-195 IU/L, females 24-170 IU/L), while the median values for the two combination regimens were slightly elevated (197 IU/L and 224 IU/L). Although, based on the limited data in NV-02B-003, increases in CK levels were more pronounced with LdT compared with LAM, there was no suggestion of a relationship between dose and CK elevations for the doses evaluated. The median CK levels at Week 52 for the LdT 400 mg and 600 mg monotherapy regimens were both within normal limits.

In the NV-02B-003 rollover study, the Applicant reports that NV-02B-010, 64 (62%) subjects experienced new-onset Grade 1-2 CK elevations on treatment: 6/19 (32%) on LAM, 27/44 (61%) on LdT, and 31/41 (76%) on combination therapy. During the second year of the study, the proportion of subjects with Grade 1-2 CK elevations in each treatment arm was similar to the first year, with the exception of LAM subjects (11%). Few subjects experienced new-onset Grade 3-4 CK elevations: 1/19 (5%) on LAM, 5/44 (11%) on LdT, and 2/41 (5%) on combination therapy. Grade 3-4 CK elevations occurred more often in the first year in the LdT group (9%) compared to the second year (5%). All Grade 3 or 4 CK elevations had declined to below Grade 3 by the next study visit. Five subjects (5%) in each treatment arm had CK elevations reported as an AE (Grade1-2,) none of which required interruption or discontinuation of study drug. No subject discontinued study therapy due to elevated CK, and no CK elevation was reported as an SAE.

MO Comments
Despite the small number of subjects on the to-be-marketed dose of LdT in both of these supporting studies, the results support the trend of increased CK elevations among subjects on LdT relative to LAM. The small sample size prohibits a quantitative comparison of the incidence of CK elevations in the supportive studies with the incidence of CK elevations in the NV-02B-007 study.

Creatine Kinase Elevations: Drug-Associated Myopathy
As a class, nucleoside analogues have been associated with specific target organ toxicities, including myopathy. Drug-induced myopathy ranges from mild myalgias with or without mild weakness to chronic myopathy with severe weakness, to massive rhabdomyolysis with acute renal failure[38] Although elevation of serum CK is often seen in muscle disease, most subjects in NV-02B-007 with CK elevations did not report muscular symptoms that might be associated with a drug-induced myopathy.

The Applicant identified AEs[39] in the pivotal trial that might specifically be associated with muscle AEs and/or rhabdomyolysis and therefore with CK elevations, and performed an analysis to determine whether these were temporally associated with CK elevations. The Applicant found that the majority of Grade 3-4 CK elevations in both treatment groups were not temporally associated with the occurrence of one of their identified muscle-related AEs; several instances of these types

[37] Table 5-28, Summary of Clinical Safety, p. 92
[38] Miller, M. Drug-Induced Myopathies. In: *UpToDate*, Rose, BD (Ed), *UpToDate*, Waltham, MA, 2006.Up-To-Date, January 20, 2005.
[39] Includes preferred terms: fatigue, myalgia, asthenia, pain in the extremities, malaise, musculoskeletal stiffness, musculoskeletal discomfort, musculoskeletal pain, myopathy, and pain.

of AEs were found within the 30-day window, but not in a uniform pattern with regard to type of AE and timing with respect to the CK elevation (see Table 7.1.3.3B).

Table 7.1.3.3B: NV-02B-007: New-Onset Grade 3-4 CK and CK-Related AEs [a]

	LdT (n=680)	LAM (n=687)	Total (n=1367)
Number of Subjects	61	22	83
Number of Episodes of Grade 3-4 CK Elevations	75	24	99
• **Occurred Within an AE**	8 (10.7)	1 (4.2)	9 (9.1)
• **Occurred Outside an AE**	67 (89.3)	23 (95.8)	90 (90.9)
• **Occurred Within an AE +/- 30 Days**	8 (10.7)	1 (4.2)	9 (9.1)
• **Occurred Outside an AE +/- 30 Days**	67 (89.3)	23 (95.8)	90 (90.9)

Source: Table 14.3.1.4.18.13, NV-02B-007 Study Report
[a] CK-related AEs as defined by the Applicant: fatigue, myalgia, asthenia, pain in the extremities, malaise, musculoskeletal stiffness, musculoskeletal discomfort, musculoskeletal pain, myopathy, and pain

These analyses indicate that most Grade 3-4 CK elevations were not temporally associated with muscle-related signs and symptoms. The Applicant also found that there were no significant differences, between the two treatment groups, in the incidence of any of these specific muscle-related AEs, in LdT and LAM recipients with Grade 1-2 or Grade 3-4 CK elevations. When this Medical Reviewer performed similar analyses examining subjects with Grade 1-4 CK elevations with a slightly different constellation of on-treatment AEs that are likely to be muscle-associated[40,41] within +/- 30 days of a Grade 1-4 CK elevation, the following proportions of subjects with CK-associated AEs were obtained:

- Grade 1-4 CK elevation: LdT (55; 8.1%) vs. LAM (42; 6.1%)
- Grade 1-2 CK elevation: LdT (48; 7.1) vs. LAM (38; 5.5%)
- Grade 3-4 CK elevation: LdT (7; 1.0%)) vs. LAM (4; 0.6%)

MO Comments
The Medical Reviewer analysis supports the Applicant's assertion that there was not a substantial difference between the treatment groups in the development of muscle-related AEs within 30 days of a Grade 3-4 CK elevation, even though a different, more muscle-specific, subset of AEs was considered. When all grades of CK elevation were considered, the potential signficiance of the two percent difference in CK-related AE incidence between the arms is difficult to interpret.

On January 26, 2006, the Applicant hosted a Telbivudine Creatine Phosphokinase Roundtable Discussion and invited several expert guests, many of whom were from academia.[42] Discussion focused largely on the physiology of CK elevation, other drugs associated with CK elevation (including daptomycin and statins), and the implications of the finding of a higher rate of

[40] There is more fatigue seen among subjects on LdT than LAM (see Common Adverse Event Table). Due to their relative lack of specificity in the context of interpreting CK elevations, both fatigue and asthenia were excluded from the Medical Reviewer analysis.
[41] Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, pain in extremity
[42] The invited attendees were John A. Faulkner, PhD, Professor of Physiology, University of Michigan Medical School; David P. Nicolau, PharmD, FCCP, Director of the Center for Anti-infective Research and Development at Hartford Hospital; Stephen Ryder, MD, Queens Medical Centre; John Bartlett, MD, Johns Hopkins University; and Gino Girardi, MD, President of BioLogica, Ltd.

CK elevations among LdT subjects relative to LAM in the NV-02B-007 study. Various panel members came to the following conclusions:

- CK elevations with LdT were different than those associated with the statins and daptomycin because it appeared that the LdT-associated CK elevations were asymptomatic.
- CK elevations with LdT (generally asymptomatic) appear similar to those observed during HIV studies with NRTIs, and are probably of little clinical significance. It was noted that the DAIDS toxicity table had been updated to raise the levels for each toxicity grade and that the one used in the GLOBE study was currently out of date.
- Group discussion on whether to discontinue therapy in patients with elevated CK levels was inconclusive as there was no clear correlation with elevated CK levels and muscle-related symptoms.
- Statin class-labeling was discussed in some detail, and it was acknowledged that this would be inappropriate as rhabdomyolysis had not been observed in the telbivudine program.
- There was uncertainty as to what labeling would be appropriate. It was also concluded that the further definition of the relationship between CK elevations and clinical signs and symptoms should be defined.
- No decision was finalized regarding the need for a clinical trial specifically evaluating CK elevations as this had been well characterized during the development program.

There were, however, a number of subjects who discontinued or interrupted study drug because of elevated CK and/or muscle-related symptoms (See Section 7.1.3.2 Adverse Events Associated with Dropouts). The Applicant updated their NDA application on September 13, 2006, in part, with the results of a database search for subjects who discontinued or interrupted study drug for an elevated CK and/or muscle-related symptom in studies NV-02B-007 (current as of 02 August 2006) and NV-02B-015 (current as of 24 August 2006). These subjects on LdT who discontinued or interrupted study drug for CK elevations, with or without associated muscle-related symptoms, merit more detailed description and are presented below. Those subjects who discontinued study drug due to an adverse event or serious adverse event associated with muscular-weakness, regardless of the CK profile, are discussed separately in the section below entitled Drug-Induced Myopathy: Muscle Weakness.

NV-02B-007—Subject # 071-043 (SAE/discontinuation)
This subject is a 24 year-old Caucasian male on LdT. He was not taking any concurrent medications at the time of the advere event. Below is a brief summary of the timing, symptoms, and management of this CK-related adverse event that ultimately resulted in study drug discontinuation.

- Screening/Baseline: The subject's CK was elevated at both Screening (298 IU/L; ULN 195 IU/L) and Baseline (222 IU/L) and remained elevated in the range of 231 to 343 IU/L through Week 32.
- Study Day (SD) 281: CK was very elevated (1886 IU/L), but the subject was asymptomatic.
- SD 337: CK level was further elevated to 2435 IU/L. The subject remained asymptomatic.
- SD 366: The subject was found to have a CK level of 4000 IU/L and complaints of moderate generalized muscle pain. He did not show any signs of a skin rash or muscle weakness.
- SD 368: LdT was interrupted.
- SD 380: Muscle pain resolved.
- SD 381: CK-MB was 34 IU/L and CK levels were 1318 IU/L.

- SD 466: Subject's CK levels had returned to normal (180 IU/L) and the event was considered resolved on that date.
- SD 529: LdT was not restarted and the subject was started on ADV
- The Investigator determined that this adverse event was reasonably or possibly related to study drug treatment.

MO Comments
The subject had an elevated CK-MB, but given the absence of cardiac symptoms, the reduced diagnostic specificity of CK-MB elevations in the context of skeletal muscle injury,[43] *it seems unlikely that myocardial toxicity occurred along with skeletal muscle toxicity and that the elevated MB fraction in this subject was a marker of drug-induced cardiac muscle injury.*

NV-02B-007—Subject # 068-021 (SAE/interruption)
This subject was a 22 year-old Caucasian male on LdT. He was not taking any concurrent medications at the time of the advere event. Below is a brief summary of the timing, symptoms, and management of this CK-related adverse event that ultimately resulted in study drug discontinuation.

- Baseline: The subject's baseline CK was normal (89 IU/L; ULN 195 IU/L).
- SD 176: The first elevation of CK (686 IU/L) was noted with mild generalized muscle weakness (subject was a competitive arm wrestler and was encouraged to discontinue).
- SD 220: CK decreased to 303 IU/L.
- SD 276: The subject experienced an important medical event of increased CK level of 1645 IU/L (ULN 179 IU/L) and some weakness and tiredness without pain or tenderness.
- SD 277: LdT was interrupted.
- SD 283: CK level had dropped to 203 IU/L (approximately the upper limit of normal for the local laboratory) and CK-MB was 20 IU/L.
- SD 287: The Investigator restarted the subject on LdT.
- SD 347: The subject's CK level was 584 IU/L (local lab) but he was asymptomatic and reported that he had stopped arm wrestling.
- SD 350: CK values were were 271 IU/L (central lab) and 409 IU/L (local lab). AST (64) and CK-MB (30 U/L; ULN 24 U/L) was also elevated. CRP was 0.1 mg/dL (ULN < 0.800 mg/dL) and ESR was within normal limits.
- SD 354: Myoglobulin levels were within normal limits and an EMG of the bilateral upper and lower extremities was normal.
- SD 365: CK-MB (19 U/L) and CK decreased to normal range (162 IU/L). The subject's CK values continued to fluctuate over time but stayed within approximately 1.5 times the upper limit of normal.
- SD 416: Subject's CK level was 214 IU/L
- SD 423: The investigator considered the event to be resolved with no residual effects and did not consider this adverse event as reasonably or possibly related to study drug treatment; he attributed the fluctuating CK levels and muscle symptoms to the subject's competitive arm wrestling.
- SD 451: The Investigator downgraded this SAE to an AE, but the Applicant maintained the SAE classification.

[43] Apple FS. "The specificity of biochemical markers of cardiac damage: a problem solved." Clin Chem Lab Med. 1999 Nov-Dec; 37(11-12):1085-9. In this article the author notes that studies reveal that CK-MB can be expressed up to 20% of total CK activity in human skeletal muscle; and therefore is not 100% specific for the heart.

MO Comments
This subject also had an elevated CK-MB, but given the absence of cardiac symptoms, the reduced diagnostic specificity of CK-MB elevations in the context of prolonged exercise[44] and skeletal muscle injury,[45] it seems unlikely that myocardial toxicity occurred along with skeletal muscle toxicity and that the elevated MB fraction in this subject was a marker of drug-induced cardiac muscle injury. It is unknown, however, if higher than average levels of exercise, in conjunction with LdT consumption, may exacerbate the risk of developing CK elevations, elevations of MB fraction and/or CK-associated symptoms. It is reassuring that the subject has been able to maintain CK levels at or close to the normal range after resumption of LdT therapy.

NV-02B-007—Subject # 025-008 (non-serious AE/discontinuation)
This subject was a 42 year-old African American male on LdT. His medical history is significant for 'CPKs elevated due to competitive body building.'

- Baseline: CK was elevated at 656 IU/L (ULN 195 IU/L) and remained moderately elevated.
- SD 274: CK rose to 1011 IU/L and the subject was discontinued from the study for the AE of 'elevated CK'. The CK declined to below baseline levels by the second month of follow-up and remained at similar levels (275-396 IU/L) until SD 448.
- The other AE of significance during the course of the study was fatigue (weak knees when climbing stairs) for which no start date was recorded but which was reported to have resolved by SD 338; this AE was not considered to be related to study drug.

MO Comments
As noted with Subject #068-021, it remains unknown, whether or not higher than average levels of exercise, in conjunction with LdT consumption, might exacerbate the risk of developing CK elevations and/or CK-associated symptoms.

NV-02B-007—Subject # 025-008 (non-serious AE/discontinuation)
This subject was a 30 year-old Chinese male without significant medical history on LdT.

- Baseline: CK was slightly elevated at 269 IU/L; ULN 195 IU/L
- SD 332 to SD 450: The subject had an AE of fatigue; roughly concurrent with this AE were two additional AEs: abdominal distension and nausea. All 3 AEs were considered related to study drug. CK levels peaked (SD 332) at 1619 IU/L (MM fraction 100% with 0% CK-MB
- SD 391: All 3AEs resulted in study drug discontinuation. CK levels dropped after study drug discontinuation, but fluctuated between normal and 413 IU/L at the 3 month follow-up visit.

NV-02B-015—Subject # 006-004 (non-serious AE/discontinuation)
This subject was a 35 year-old Chinese male on LdT. His medical history was significant for myocardial ischemia.

- Baseline/Screening: Normal CK levels.
- SD 230: CK levels increased to1104 IU/L; ULN 195 IU/L.

[44] Thompson GR. Hazards of running a marathon: Creatine kinase MB can be raised without myocardial infarction. BMJ 1997; 3 14:1023-1025
[45] Apple FS. "The specificity of biochemical markers of cardiac damage: a problem solved." Clin Chem Lab Med. 1999 Nov-Dec; 37(11-12):1085-9. In this article the author notes that studies reveal that CK-MB can be expressed up to 20% of total CK activity in human skeletal muscle; and therefore is not 100% specific for the heart.

- SD 308: The subject had AEs of "aching pain in legs" and fatigue, both of which were considered related to study drug.
- SD 367: CK levels peaked at 1389 IU/L.
- SD 378: Study drug was discontinued due to the musculoskeletal AE.
- SD 492: The musculoskeletal AE was considered resolved and by the 1 month follow-up visit, CK levels had normalized.

NV-02B-007—Subject # 105-012 (non-serious AE/interruption, then discontinuation)
The subject was a 27 year-old Chinese male, without significant medical history, on LdT.

- SD 225: Muscular soreness was noted on physical exam (CK was normal) and reported as an AE.
- SD 260: An AE of fatigue was reported (CK rose to 249 IU/L; ULN 195 IU/L)
- SD 364 through SD 376: Although neither of these AEs was considered to be related to study drug, both AEs had an action taken of 'study drug interrupted'. CKs remained elevated in the range of 325- 597 IU/L. By the end of this period (SD 376), muscular soreness and fatigue were reported as 'relieved'.
- SD 589: CK level peaked at 1405 IU/L.
- SD 477: Muscular soreness was reported as changed from Grade 2 to Grade 1.
- SD 600: Study drug was discontinued due to 'subject, investigator, or sponsor request' and the CK levels decreased to 309 IU/L by the month 4 follow-up visit.
- SD 652: Resolution date for the AE of muscular soreness.
- SD 620: Resolution date for the AE of fatigue.

NV-02B-007—Subject # 079-004 (non-serious AE/discontinuation)
This subject was a 31 year-old Asian male on LAM with a medical history notable for diabetes mellitus and "heel pain and weakness" with low blood sugars.

- SD 416: Initial AEs of CK elevations were noted (CK 413 IU/L; ULN 195 IU/L).
- SD 476: CK was further elevated to 3610 IU/L.
- SD 477: A concurrent AE of 'mild fatigability in both legs', with normal tone, strength, and reflexes on physical exam was noted.
- SD 479: Study drug was discontinued due to the elevated CK. Both the CK elevations and the accompanying AE resolved off study drug.

In addition to the cases described above, narratives were reviewed for subjects on LdT who interrupted SD due to AE of CK elevation, both with and without associated clinical symptoms. Only one of these study drug interruptions resulted in permanent study drug discontinuation as described above in the narrative for Subject # 105-012. Although not all subjects had resolution of their CK elevations, most have resumed study drug treatment, completed the NV-02B-007 study and rolled over into the omnibus study (NV-02B-022), continuing on study drug.

MO Comments
This Medical Reviewer does not agree with the reason assigned to Subject # 105-012 for study drug discontinuation. The time course and symptomatology described in the narrative suggest that study drug was discontinued due to the ongoing adverse events. Overall the narratives describe cases of CK elevation with associated muscle symptomatology without explicit muscle weakness or findings consistent with myopathy.

As shown earlier in Section 7.1.3.2, Adverse Events Associated with Dropouts, more subjects on LdT than LAM discontinued or interrupted study drug due to CK elevations, most of whom experienced associated symptoms. Throughout the LdT development program, only one subject on

LAM (007-079-004 described above) is known to have discontinued study drug due to a CK elevation. The higher frequency of study drug discontinuations due to CK elevation for LdT subjects may be a consequence of the higher frequency of CK elevations among subjects on LdT (LdT: 9%; LAM 3.2%), resulting in more absolute numbers of subjects on LdT with CK-associated clinical adverse events. Or the CK-related discontinuation rate among LdT subjects may be due to some LdT-specific toxicity resulting in more discontinuations among those subjects with CK elevations, although this is less likely. A comparison of clinical adverse events, with particular attention to the frequency of musculoskeletal (excluding adverse events suggestive of explicit muscle weakness) adverse events occurring within 30 days of CK elevations, revealed only a slight difference in the occurrence of AEs between subjects with CK elevations on study drug and on the comparator drug LAM. (See Section on Common Adverse Events). For the few subjects who developed adverse events associated with muscular weakness, with or without associated CK elevations, however, the consequences of LdT-associated myopathy were more severe. This occurred more commonly among LdT subjects than LAM subject and will be discussed further in the section discussing muscular weakness below.

The conclusions drawn by the participants in the Idenix-sponsored Telbivudine Creatinine Phosphokinase Roundtable Discussion in January, 2006 were based on the premise that the CK elevations were asymptomatic. Given the data presented above on study drug discontinuations and interruptions due to CK elevations and associated CK-related symptoms described above and the subjects who ultimately discontinued or interrupted study drug due to a myopathic adverse event with associated CK elevations that will be described in the next section (Drug-Associated Myopathy: Muscular Weakness), the recommendations of the Roundtable Discussion appear outdated. Much of this data was not available in January, 2006 and was uncovered through an LdT safety database search, conducted by Idenix, in August of 2006.

Given the much lower incidence of CK-related symptoms among subjects with CK elevations on LdT (or LAM) and the imperfect relationship between the timing and severity of the CK elevations and the development of symptoms, there does not seem to be a significant role for routine CK monitoring in asymptomatic patients (that are capable of reporting symptoms) in the clinical care of patients with HBV. As we gain more clinical and trial experience with LdT and are better able to characterize the risk for the development of CK-related symptoms, a role for routine CK monitoring may evolve.

Drug-Associated Myopathy: Muscular Weakness

As noted above under Creatine Kinase Elevations: Drug-Associated Myopathy, there have been a number of subjects who discontinued or interrupted study drug because of CK elevations and/or CK-related symptoms. For muscle weakness, however, and other symptoms specific to myopathy, there appears to be an association with LdT in the Phase 3 development program. Medical Reviewer examination of the pooled dataset for studies NV-02B-007 and NV-02B-015, provided in the 120-Day NDA Safety Update, revealed minimal differences in the occurrence of AEs (Grade 1-4) that might be associated with a muscular disease process[46] between the study arms (LdT: 10.3%; LAM: 9.4%). The median time to onset of these symptoms was 273 days (range 1 to 730 days).

When reviewing datasets provided with the original NDA submission for general muscle-related adverse events that might be associated with a myopathy[47] that occurred at the time, or within 30

[46] Includes Preferred Terms: back pain, muscle cramp, muscular weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, pain, pain in extremity, polymyositis, tenderness.
[47] Includes Preferred Terms: back pain, muscle cramp, muscular weakness, musculoskeletal chest pain,

days, of a Grade 3-4 CK elevation, LAM and LdT groups had relatively similar frequencies of related adverse events, as described above under Creatine Kinase Elevations: Drug-Associated Myopathy. When examining the subjects with muscle-related adverse events that were explicitly associated with muscle weakness,[48] there were a greater proportion on the LdT arm (7 subjects; 0.8%) than the comparator LAM arm (2 subjects, 0.2%). The median time to onset of symptoms was 261 days (range 27 to 325 days). These specific AEs were predominantly Grade 1-2 in severity.

As noted earlier, the Applicant updated their NDA application on September 13, 2006 with the results of a database search both for subjects who discontinued or interrupted study drug for an elevated CK and/or muscle-related symptom in studies NV-02B-007 (current as of August 2, 2006) and NV-02B-015 (current as of August 24, 2006) and for SAEs suggestive of a muscle effect of LdT (current as of August 31, 2006.) They identified a total of 2 subjects with SAEs suggestive of a myopathy with muscular weakness, both of whom were reported in the original submission and the 120-day safety update. In addition, they identified 3 subjects on LdT with adverse events resulting in study drug discontinuation or interruption due to a muscle-related adverse event associated with myopathy with muscular weakness.

These five subjects on LdT with myopathy/muscular weakness-associated AEs or SAEs merit more detailed descriptions and are presented below.

NV-02B-007--Subject # 012-001 (SAE/discontinuation)
This subject is a 57-year old Chinese male on LdT with history of HBeAg-positive chronic hepatitis B and atrial fibrillation. His medications included ticlopidine, atenolol and a multivitamin. Below is a brief summary of the timing, symptoms, and management of his myopathic adverse event.

- SD 278: The subject presented with crampy abdominal pain and increased stool frequency.
- SD 309: He underwent esophagogastroduodenoscopy (EGD) which revealed *H. pylori*-related ulcers with severe chronic active gastritis. He was started on omeprazole, amoxicillin, and clarithromycin. His laboratory findings were:
    - Erythrocyte sedimentation rate (ESR): 30-40 mm/L; CK: 645 IU/L; mildly elevated aldolase: 10.3
- SD: 327: The subject continued to have abdominal pain, peripheral muscle pain, generalized weakness, and difficuly arising from a squatting position. His physical examination revealed weight loss and decreased proximal strength and his CK had risen to 731 IU/L.
- SD: 327: Ticlopidine was stopped and the subject was diagnosed with a generalized myositis possibly related to the study drug. His EMG suggested a predominantly myopathic process and a muscle biopsy revealed myofibrillary degeneration. The subject's CK levels were again moderately increased at 458 IU/L.
- SD: 338: LdT was discontinued because the subject was symptomatic and not restarted because he met discontinuation criteria for efficacy. The omeprazole was also stopped around this time.
- After the removal of study drug (and omeprazole), the subject experienced improvement in weakness, with a progressive improvement of his muscle pain, normalization of his CK levels. He continued to experience subjective and objective improvement over subsequent months.

musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, pain, pain in extremity, polymyositis, tenderness.
[48] Includes Preferred Terms: myositis, myopathy, muscular weakness, polymyositis

- One year after removal of study drug, the subject had resolution of muscle pain, normal muscle strength and tone, normalization of aldolase and lactase, but still had mild type II atrophy on EMG. His CK remained slightly elevated at 233 IU/L.
- The Investigator considered this adverse event as possibly or reasonably related to the study drug.

MO Comments
Omeprazole and other proton pump inhibitors have been associated with polymyositis and other myopathies based on reports in post-marketing data and in the medical literature.[49] *The subject started omeprazole after the onset of pain, but approximately two weeks prior to the onset of proximal weakness and it therefore a confounder in the assessment of causality for this unspecified myositis. This Medical Reviewer agrees with the Investigator's assessment and considers it very likely that the study drug played a causal role in the development of this subject's constellation of myopathic adverse events. It is notable that the subjects symptoms improved after study drug discontinuation.*

NV-02B-015—Subject # 010-023 (SAE/continuation):
This subject is a 20-year old Chinese male with HBeAg-positive chronic hepatitis B on LdT. He was not taking any concomitant medications. Below is a brief summary of the timing, symptoms, and management of his myopathic adverse event.

- SD 297: The subject presented with pain in the upper abdomen, chest, arms and legs. He also had edema in both feet and difficulty climbing stairs.
- SD 323: He was found to have an elevated LDH (303 U/L; ULN 250 U/L), and CK (586 U/L; ULN 215 IU/L). His CK profile prior to the onset of symptoms ranged from 853 IU/L to 239 IU/L.
- SD 324: An EMG revealed a myopathic process. The subject was hospitalized and diagnosed with polymyositis.[50] He was treated with prednisilone (initial dose 60 mg/d), Vitamin B12, ATP, and Coenzyme A, with improvement in edema and limb power, despite continued pain. The subject was continued on study drug throughout the SAE. His work-up included testing for anti-ENA antibodies (Sm, RNP, SS-A, SS-B, JO-1, Scl-70), which were negative, anti ds-DNA and ss-DNA were <6.3 IU/mL, and ESR was 4 mm/L. CK was normal on SD 332.
- SD 380: A muscle biopsy revealed revealed partial muscle fibrosis, mild muscle atrophy, and partial rhabdomyolysis (possible translation errors).
- SD 475: The subject had continued, but mild weakness of all four limbs, no muscle pain and was able to get around without assistance. Mild muscle wasting of the four limbs was noted on exam, however, without loss of sensation.
- SD 505: He was able to walk without pain.
- SD 517: The subject had remained on both study drug and prednisone throughout this adverse event and hospitalization. He was ultimately discharged from the hospital on prednisone 20mg/day seven months after presentation initial presentation.
- The Investigator did not consider this adverse event possibly or reasonably related to the study drug.

[49] Clark DWJ and Strandell J. "Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors?" European Journal of Clinical Pharmacology. Vol 62 (6): 473-479. June 2006. Online abstract: http://www.springerlink.com/content/388n720v0w7188x6/
[50] Per the Applicant, Subject #010-023 was hospitalized to facilitate his work-up since he lived in a remote area within China.

MO Comments
This Medical Reviewer agrees with the Applicant's recent suggestion that this subject's diagnosis is unclear. There was no clear demonstration of inflammation on muscle biopsy, a normal ESR and an absence of other markers indicative of myositis. Biopsy-confirmation of his diagnosis is needed. While the response to steroids and the clinical history might suggest a reversible component, the proximal muscle weakness is a nonspecific finding and, as the Applicant noted, the reported lack of lymphocytic infiltrates on the muscle biopsy report suggests that other etiologies should be considered. The Applicant is having the muscle biopsy report translated independently and is attempting to find a way to have the original biopsy slides read by an independent expert histopathologist with expertise in musculoskeletal diseases. This Medical Reviewer also agrees with the Applicant's assertion that the term rhabdomyolysis used in the biopsy report may reflect a translational error as the subject's clinical picture is not consistent with rhabdomyolysis. While the Investigator did not consider this SAE to be related to the SD, the clinical picture suggests that the subject may have had a drug-associated myopathy, complicated by ongoing administration of study drug and steroids.

NV-02B-007—Subject # 054-031 (non-serious AE/discontinuation):
This subject is a 31-year old (90 kg) Korean male with HBeAg-positive chronic hepatitis B on LdT. He was discontinued from study drug in the second year of the pivotal study.

- SD 0: At baseline and screening, this subject's physical examination and CK were within normal limits.
- SD 226: The subject was noted to have persistent CK elevations (CK = 323 IU/mL; ULN 170 IU/mL)
- SD 568: The ongoing CK elevations dating back to SD 226, now peaked at 2934 IU/mL (Grade 4 and recorded as AE).
- SD 583: Study drug was discontinued approximately 1 yr after onset of the persistent CK elevations due to a diagnosis of myopathy. The date of onset for the myopathy is unknown. The subject was not taking any concomitant medications at the time of the occurrence of myopathy. Other AEs that overlapped with the report of myopathy were fatigue and anorexia.
- An EMG was performed, revealing generalized myopathy (date of onset unknown)
- SD 616: The subject was discontinued from the study and the myopathy subsequently resolved. His CK was 283 IU/L around this time.
- The Investigator considered this adverse event as reasonably or possibly related to study drug.

MO Comments
Given the EMG findings and clinical picture, however, it is evident that this subject had a myopathy, likely LdT-related, that improved with LdT discontinuation.

NV-02B-007—Subject # 057-123 (non-serious AE/discontinuation)
This subject is a 60-year old Maori/Aboriginal male subject on LdT with a medical history notable for diabetes mellitus (DM) and HBeAg-negative chronic hepatitis B. His diabetes was treated with gliclazide.

- SD 0: This subject's CK was elevated at Screening: 458 IU/L; ULN 195 IU/L.
- On approximately SD 275, the subject was noted to have muscle weakness, muscle tenderness, and weight loss[51]. His CK ranged from 670-3890 IU/L during these AEs,

[51] While the month and year of symptom onset are known (January, 2005), the day of onset of symptoms is unknown. Assuming that symptoms started on January 1, 2005, the subject would have been on study drug for 275 days at the time

including tenderness over his anterior thighs. He had received short-term treatment with claratyne, augmentin (amoxicillin and clavulanate potassium) within the month prior to the onset of symptoms.

- SD 447: The subject was discontinued from study drug for Grade 1 myalgia, Grade 1 myositis and decreased weight. He was subsequently started on ADV.
- This subject's muscle symptoms resolved approximately 15-16 months after study drug discontinuation. His CKs gradually decreased during follow-up visits, reaching the normal range by his 3 month follow-up (174 IU/L).
- The Investigator considers these adverse events as not reasonably or possibly related to study drug.

MO Comments
This subject was found to have muscle weakness, tenderness and weight loss and subsequently diagnosed with myositis. Without biopsy confirmation to confirm the specific diagnosis of myositis, or any other markers of inflammation, it is not possible to confirm this diagnosis. This Medical Reviewer believes that this case likely represents a case of LdT-associated myopathy.

NV-02B-007—Subject # 132-002 (non-serious AE/interruption)
This subject is a 22 year old Indian/Middle Eastern female with HBeAg-positive chronic hepatitis B on LdT.

- SD 0: This subject's CK levels were normal at Baseline.
- She experienced AEs of 'CK elevation' and 'weakness of both lower limbs' which resulted in study drug interruption (date and duration unknown). Both AEs were considered resolved by the end of the study. The subject's first CK elevation was noted by week 24 (178 IU/L; ULN 170 IU/L) and remained elevated until the end of the study (Week 104), although they were intermittently within the normal range. Her peak CK was 1192 IU/L at Week 52, but most CK elevations were Grade 1-2.
- In addition the subject had an AE of 'breathlessness' that started after approximately one year on LdT and lasted for almost two months.
- She continued on study drug for the remainder of NV-02B-007 and subsequently enrolled in the omnibus study (NV-02B-022) study. She has completed at least 16 weeks of NV-02B-022 (as of July 19, 2006).

MO Comments
Although the Investigator attributes causality to the study drug in only two of the five cases described above, this Medical Reviewer considers all five events as reasonably or possibly related to study drug. There seems to be an emerging pattern of a cumulative toxicity resulting in myopathy for subjects on LdT. The myopathy occurs with LdT use greater than 8-10 months. Looking beyond the subjects described above, there is, overall, a greater proportion of adverse events related to muscle weakness on the LdT arm (7 subjects, 0.8%) than on the LAM arm (2 subjects, 0.2%) for the NV-02B-007. No subjects on LAM discontinued or interrupted study drug due to an adverse event related to muscle weakness in either the Chinese (NV-02B-015) or American (NV-02B-007)LdT registrational trials.

The predisposing factors, if any, for the development of myopathy with chronic LdT use are unknown. Only subject 012-001 was on a concomitant medication that might have a clear association with myopathy. Most of the other subjects were not on medications that might be implicated in the myopathy. The subjects represented a very broad demographic, including both

of symptom onset.

male and female subjects, ages 20 to 60, obese and normal weights, from a variety of ethnic backgrounds, including Chinese, Korean, Maori/Aboriginal, and Indian/Middle Eastern. Perhaps it is notable that no Caucasian subjects developed myopathy. There are too few subjects with myopathy to draw conclusions regarding predisposing factors.

The possible mechanism of toxicity is also unclear. While preclinical testing for mitochondrial toxicity was negative, there were limitations to the assessment. The Microbiology reviewer is recommending postmarketing commitments for additional in vitro testing for mitochondrial toxicity in growing muscle cells, cell lines and primary cells, and primary hepatocytes, with appropriate controls to validate the results. It is difficult to be certain whether or not a mitochondrial toxicity is playing a role in this adverse event profile. Perhapse there is toxicity to actin and/or myosin? There is insufficient data to fully characterize the etiology or mechanism of action guiding this drug-associated myopathy, occurring among LdT recipients with extended use.

There is also insufficient data to determine whether or not the subjects who developed drug-associated myopathy share a common predisposing risk factor. There is a large background of CK elevations in the study, increasing the difficulty in understanding the relationship between the myopathy and the CK elevations. As noted earlier, there is an imperfect relationship between the timing and severity of the CK elevations and the development of muscle weakness.

Further characterization of this toxicity will occur through the Microbiology post-marketing commitments described above and careful and systematic protocol-specified collection of data for the subjects with myopathy in the ongoing LdT studies.

Drug-Associated Myopathy: Rhabdomyolysis

There have not been any known clinical cases of rhabdomyolysis, with or without renal failure, in the LdT development program. Formal analysis for rhabdomyolysis did not occur routinely among subjects with CK elevations during the development program, including pivotal trial. [52] Also, renal failure was not reported as an adverse event among subjects in the first year of treatment. Among subjects with Grade 1-4 CK elevations and adverse events[53] that might be associated with rhabdomyolysis, the median Creatinine (Cr) was within normal limits. In addition, there was one LAM-treated subject for whom "dark urine" was reported as an AE. While this subject also had a Grade 1 CK elevation, he did not have other adverse events that might be associated with rhabdomyolysis. The other 4 subjects (2 LdT; 2 LAM) with hematuria reported as an AE also did not have other adverse events that might be associated with rhabdomyolysis, although two of them did have grade 1-2 CK elevations (1 LAM and 1 LdT).

MO Comments

Although formal evaluation for rhabdomyolysis was not conducted in most subjects with CK elevations, the review of the safety database and clinical narratives for subjects who discontinued or interrupted study drug due to CK elevations suggest that this diagnosis was unlikely among subjects on either study treatment arm.

ALT Flares and Hepatic Adverse Events

Acute exacerbations of hepatitis (ALT flares) represent a critical issue in the safe treatment and management of patients with chronic HBV infection. ALT Flares have been described during treatment with all of the approved anti-HBV drugs and after discontinuation of these drugs. The

[52] Urine myoglobin was not routinely checked among study subjects with CK elevations and CK-related symptoms.
[53] Occurring within 2 months of CK elevations

Applicant captured data regarding ALT flares according to four categories and analyzed them by treatment group in terms of grade, timing, and association with HBV levels. The first two categories described below were intended to detect patients with mild-to-moderate ALT flares. The third category (with ALT > 500 IU/L) was intended to capture clinically worrisome ALT flares, for which most providers would schedule follow-up evaluation. The fourth category (ALT flare with a bilirubin elevation) was intended to detect ALT flare events associated with a biochemical sign of hepatic decompensation (e.g. hyperbilirubinemia). These four categories were initially used in the LAM Phase 3 trials and are described below:
ALT Flare Category 1: ALT elevation ≥ 2× Baseline (and ≥ 2× ULN)
ALT Flare Category 2: ALT elevation ≥ 3× Baseline (and ≥ 3× ULN)
ALT Flare Category 3: ALT elevation ≥ 500 IU/L and ≥ 2× Baseline
ALT Flare Category 4: ALT elevation ≥ 2× Baseline with bilirubin ≥ 2× Baseline (and ≥ 2× ULN)

Table 7.1.3.3 C: NV-02B-007: Summary of On-Treatment ALT Flare Phenomena by HBeAg Status and Treatment Group

ALT Flare, n (%)	**HBeAg Positive**		**HBeAg Negative**		
	LdT (n=445)	**LAM** (n=455)	**LdT** (n=235)	**LAM** (n=232)	**Totals** (n=1367)
ALT Flare Category 1	36 (8.1)	33(7.3)	5(2.1)	6(2.6)	80 (5.9)
ALT Flare Category 2	17 (3.8)	19(4.2)	0	9(3.9)	45 (3.3)
ALT Flare Category 3	16(3.6)	26 (5.7)	2(0.9)	3(1.3)	47 (3.4)
ALT Flare Category 4	0	3 (0.7)	0	0	3 (0.2)

Source: Tables 12-13, 12-14, and 12-15 in the NV-02B-007 Full Clinical Study Report

Table 7.1.3.3 D: NV-02B-007: Summary of Clinically Significant On-Treatment ALT Flare Phenomena by Treatment Group

ALT Flare, n (%)	**LdT** (n=680)	**LAM** (n=687)	**Totals** (n=1367)
ALT Flare Category 3	18(2.6)	29 (4.2)	47(3.4)
ALT Flare Category 4	0	3 (0.4)	3 (0.2)

Source: Tables 12-13, 12-14, and 12-15 in the NV-02B-007 Full Clinical Study Report

Clinically significant ALT flares (Categories 3 and 4) were also more common among LAM subjects, as shown above in Table 7.1.3.3 D. ALT flares were more common among both LAM and LdT-treated HBeAg-positive subjects.

More recently developed AASLD clinical treatment guidelines for Hepatitis B[54] use slightly different criteria to identify ALT flare events. These criteria are: aminotransferase elevation ≥ 2× Baseline (and ≥ 10 × ULN). NDA reviews for recent anti-HBV medications (ETV) have used these ALT flare criteria. For consistency with the ETV review, this Medical Reviewer identified ALT flares using the AASLD criteria for purposes of comparison.

[54] Lok ASF, McMahon BJ. AASLD Practice Guidelines: Chronic Hepatitis B. Hepatology. 2001 Dec; 34(6): 1225–1241.

Table 7.1.3.3 E: NV-02B-007: Summary of On-Treatment ALT Flare Phenomena by HBeAg Status and Treatment Group using AASLD Criteria

ALT Flare, n (%)	**HBeAg Positive**		**HBeAg Negative**		
	LdT (n=445)	**LAM** (n=455)	**LdT** (n=235)	**LAM** (n=232)	**Total** (n=1367)
ALT Flare –AASLD Criteria	20 (4.5)	32 (7.0)	2 (0.9)	3 (1.3)	57 (4.2)

Source: Tables 4-1., 4-2, 4-3, and 4-4 in the Response to Clinical Comments, NDA 22-011, Sequence 0018.

Table 7.1.3.3 F: NV-02B-007: Summary of On-Treatment ALT Flare Phenomena by Treatment Group using AASLD Criteria

ALT Flare, n (%)	**LdT** (n=680)	**LAM** (n=687)	**Totals** (n=1367)
ALT Flare –AASLD Criteria	22 (3.2)	35 (5.1)	57 (4.2)

Source: Tables 4-1., 4-2, 4-3, and 4-4 in the Response to Clinical Comments, NDA 22-011, Sequence 0018.

The incidence of ALT flares was slightly higher in the HBeAg-positive treatment group, when using the AASLD definition compared to the incidence found using the protocol specified ALT categories described above. There was no change to the results for HBeAg-negative subjects. The majority of ALT flares, using either flare definition, occurred in the first 24 weeks of treatment compared to the subsequent 24 weeks of the study. ALT flares also occurred at a similar rate between treatment arms through Week 24. The later ALT flares (after Week 24), although fewer, occurred more commonly among LAM subjects. LAM subjects also had more severe ALT flares than LdT subjects, based on available data.

Based on the Applicant's exploratory analyses of the relationships between ALT flares (protocol-specified definition), HBV DNA levels and other viral parameters for NV-02B-007, ALT flares were often associated with the Viral Breakthrough and evidence of Treatment Failure (as defined in the NV-02B-007 protocol). Grade 3-4 ALT flares during the first 24 weeks of treatment were also noted among subjects with HBV DNA reductions greater than 4 log10 copies/mL. As expected, ALT flares led to study drug discontinuation. This occurred more commonly among LAM subjects. The only LdT subject who experienced a Grade 3-4 ALT flare and discontinued treatment officially discontinued due to a pregnancy (Subject # 100-001).

The risk of exacerbation of hepatitis with discontinuation of therapy is well-known and has been described with other anti-HBV treatments. There is very limited data from NV-02B-007 and NV-02B-015 to estimate the risk of hepatitis B exacerbation after treatment discontinuation. The numbers of subjects with data are small and the data that are available are complicated by differing durations of post-treatment follow-up. They do suggest, however, as shown below in Table 7.1.3.3 G, that persons who discontinue therapy may be at increased risk for a post-treatment hepatitis flare relative to persons who go onto another form of anti-HBV treatment.

Table 7.1.3.3 G: NV-02B-007 and NV-02B-015: Summary of ALT Flare Phenomena among Off-Treatment Subjects by HBeAg Status andTreatment Group using AASLD Criteria (as of Aug 2006)

AASLD ALT Flare, n (%)	**HBeAg Positive**		**HBeAg Negative**		
	LdT (n=69)	**LAM** (n=71)	**LdT** (n=14)	**LAM** (n=26)	**Total** (n=180)
Off-Treament ALT Flares	4(5.8)	5(7.0)	1 (3.8)	1 (7.1)	11 (6.1)
	LdT (n=59)	**LAM** (n=49)	**LdT** (n=11)	**LAM** (n=12)	**Total** (n=131)
Off-Treament ALT Flares, excluding subjects who switched to other anti-HBV therapies	4 (6.8)	2(4.1)	1(9.1)	1(8.3)	8 (6.1)

Source: Tables 4-1 and 4-3 in the Response to Clinical Comments, NDA 22-011, Sequence 0018.

Safety data was also reviewed to evaluate the occurrence of other clinical hepatic events or other laboratory abnormalities consistent with worsening liver function. Clinical AEs related to the hepatobiliary system or to hepatic (laboratory) investigations reported as AEs were tabulated. While receiving study treatment, 13 LAM subjects and 15 LdT subjects reported a clinical AE related to the hepatobiliary system, while receiving study treatment. The most common clinical AE reported was "hepatic pain" reported in 5 subjects on LAM and 4 LdT subjects, followed by perihepatic discomfort in 2 subjects on LAM and 3 subjects on LdT. These preferred terms were captured under hepatic/RUQ pain in Table 7.1.5.4 A, describing common adverse events. A total of 5 subjects experienced non-malignant hepatobiliary SAEs while on study treatment: 3 LdT subjects and 2 LAM subjects. These events included: acute cholecystitis, gallbladder perforation, hepatic lesion in LdT subjects and acute hepatitis E and a Hepatitis B exacerbation in LAM subjects. Hepatic malignancies occurred in 5 subjects: 2 LdT subjects and 3 LAM subjects. All were identified as malignant, except for three hemangiomas identified in one LdT subject and a liver nodule identified in one LAM subject.

MO Comments

The data suggest that patients who take LdT will be at risk for ALT flares while on-treatment and also if they discontinue treatment. While this risk appears to be less than that associated with LAM use, the LdT label will be modified to include language warning patients against abrupt discontinuation of anti-HBV therapy. Similar language is reflected in the Patient Package Insert.

Amylase and Lipase Elevations

As was seen in the LAM and ADV Phase 3 clinical trial programs, a few percent of subjects in the LdT trials had asymptomatic amylase or lipase elevations. These elevations occurred more commonly in LAM-treated subjects than LdT-treated subjects (See Section 7.1.5, Common Adverse Events).

One case of mild, self-limited pancreatitis occurred in a diabetic subject on LdT (Subject # 068-004) during Week 8 of NV-02B-007. Although this adverse event was reported as mild pancreatitis, the subject did not have abdominal pain and was diagnosed based only on an elevated lipase. He was found to have gallstones on abdominal ultrasound. The Investigator considers this adverse event as not reasonably or possibly related to study drug.

An additional case of acute pancreatitis in the omnibus study (NV-02B-022) was reported as a follow-up 15-Day IND Safety Report on August 16, 2006. Ths subject was a 49 year old male subject on LdT 600mg without previous history of pancreatitis or hyperamylasemia (previously enrolled in the pivotal trial, NV-02B-007). He was hospitalized with acute pancreatitis with symptoms of vomiting, bloating and abdominal pain after 95 days of study drug in the NV-02B-022 (SD 823, including time in pivotal trial). His lipase on admission was 475 U/L (normal range: < 115 U/L), and bicarb 29mmol/l (normal range: 23-29 mmol/l). The subject was not taking alcohol or new medications and had an ultrasound without evidence of obstructing stones. In addition, 38 days prior to hospitalization, the subject had also been started on ADV due to phenotypic drug resistance (increased HBV DNA level of > 1 log). The event resolved on NV-02B-022 Study Day 97 with amylase returning to within normal limits. Further workup with MRCP revealed that the subject had pancreas divisum. The Investigator felt that the cause of the pancratitis is unknown and may have been due to LdT, ADV or pancreas divisum. The subject remains on both LdT and ADV.

MO Comments
This Medical Reviewer agrees with the Applicant that the case of pancreatitis described for subject # 068-004 in the NV-02B-007 is not reasonably or possibly related to the study drug. This Medical Reviewer also agrees that the cause of pancreatitis for Subject # 031-011 may be LdT, ADV, or pancreas divisum. Pancreatitis is a known class-related effect associated with nucleoside and nucleotide analogues.

Lactic Acidosis
Lactic acidosis, sometimes accompanied by hepatic steatosis and/or pancreatitis, has been associated with the use of nucleoside analogues in the treatment of HIV infection. The syndrome has been attributed to inhibition of mitochondrial DNA polymerase (γ polymerase). For this reason, all of the HIV nucleoside reverse transcriptase inhibitors and the HBV nucleoside analogues, LAM, ADV, and ETV, have all been labeled with a boxed warning describing the possible occurrence of lactic acidosis. There has not been a prospective evaluation, during the Phase 3 registrational trial, for increased lactate or lactic acidosis. A review of the adverse event database for the pivotal phase 3 trial did not reveal any cases of lactic acidosis recorded as an adverse event. Serum bicarbonate, potassium, glucose were not included among the laboratory testing prescribed in the NV-02B-007 protocol.

MO Comments
Given the association between nucleoside analogues and lactic acidosis, it is unclear why the Applicant did not include, at least, testing for bicarbonate as part of routine laboratory collection for subjects in the pivotal trial.

7.1.4 Other Search Strategies

Additional searches were performed by the FDA to evaluate safety signals observed in the preclinical studies, in addition to safety signals observed in the clinical studies.

Neuropathy
Spinal cord and sciatic axonopathy was noted in all LdT dose groups (including controls) in monkey studies. The mechanism of axonal injury is unknown, particularly since the control primates also had similar lesions. In addition, there were more sciatic lesions in high dose in high dose (1000 mg/kg/day) female monkeys and more spinal axonapthic lesions in high dose (1000

mg/kg/day) male monkeys. The Applicant solicited independent pathology reviews, but neither the independent pathologist nor the study pathologist could confirm a role for LdT in enhancing the incidence of the focal axonal lesions. Since the same lesions were also seen in control animals, it was not possible to attribute causality to LdT. Peripheral neuropathy was also absent from other species and pharmacology studies did not show a signal for LdT and peripheral neuropathy (LdT is not able to become a substrate for DNA polymerase α, β and γ).

In clinical studies with LdT, the Applicant did not find evidence for peripheral neuropathy in the Phase 1 trials. In the Phase 2b trial, NV-02B-003, one subject discontinued from the study due to an AE of possible drug-induced neuropathy of mild intensity (Subject # 13-12). The case is described below:

NV-02B-003: Subject # 13-12: This subject was a 21-year old Asian male who developed numbness in the toes on both feet on Study Day 222, resulting in withdrawal from the study. The subject was also noted to have a CK of 699 IU/L (normal range: 24-195 IU/L). Prior CK results had been in the normal range. Repeat CK testing, four days later, revealed a CK of 1264 IU/L. Subsequent neurology consultation included EMG (normal) and nerve conduction studies, could not exclude drug-induced neuropathy. In the opinion of the investigator, the neuropathy NOS was mild in intensity (Grade 1) and reasonably or possibly related to study drug. The subject was started on fundamine E, a nutritional supplement. CK remained elevated for the next four months, gradually decreasing to normal, in follow-up month 3. At a further consultation with the neurologist, approximately seven months after the last dose of study medication, the subject's CK was noted to be normal; there was no numbness or ankle pain and the subject was discharged with no further follow-up required. The subject refused further EMG and nerve conduction tests.

The Applicant also did not find evidence for an increased incidence of peripheral neuropathy among LdT subjects in NV-02B-007, the global Phase 3 registration trial. Analysis of electronic listings dataset, AE, for NV-02B-007 by this Medical Reviewer found a slight increase in the frequency of sensory symptoms[55] among LdT subjects when compared to subjects on LAM in NV-02B-007 (3.4% of LdT subjects versus 1.9% of LAM). Review of the Clinical Summary Document for the 120-Day Safety Update also did not reveal any additional cases of peripheral neuropathy among LdT subjects in the clinical development program.

MO Comments
Since the sciatic and spinal lesions were also seen in control animals,, the preclinical neuropathic findings are of limited severity and significance. It is difficult to ascertain the causality of the peripheral neuropathy noted in Subject 13-12 in NV-02B-003 because the subject was receiving combination treatment with LAM and LdT. The concurrence of the peripheral neuropathy with an elevation in CK is suspicious, but not conclusive, since musculoskeletal complaints and findings were not recorded with the AE. While there does not seem to be a notable increase in the prevalence of neuropathy among LdT subjects, when compared to LAM, peripheral neuropathy is a known side effect of LAM. This subject's neuropathy may be related to LAM, LdT, or both.

The slight increase in sensory symptoms among subjects on LdT is of unknown significance, but is due largely to a difference in the frequency of dysgeusia between the treatment arms (LdT: 1.2% versus LAM: 0.2%). Other preferred terms evaluated in this search category had a much smaller rate of difference between the treatment arms.

[55] This search includes the preferred terms: dysesthesia, sensory loss, intercostal neuralgia, dysgeusia, paraesthesia oral, neuropathic pain, polyneuropathy, sciatica, paraesthesia, hypoaesthesia, hypoaesthesia oral, neuralgia and sensation of heaviness.

Nephropathy

LdT may have been related to the death of some rats in the long-term oral gavage carcinogenicity study (104 weeks), due to a slightly higher incidence of nephropathy-related deaths in the 1000 and 2000 mg/kg/day male rates and the 2000 mg/kg/day female rats compared to concurrent male and female controls. Chronic progressive nephropathy (CPN) occurs spontaneously and often in older Sprague-Dawley rats, but the shortened lifetime in the highest dose group (2000 mg/kg/day), which exceeded the lifetime of rats in the control and other dosing groups raises questions regarding the role of LdT in the development of this renal toxicity. While CPN should be considered a specific disease in rats and not just a manifestation of the aging process, its pathogenesis is not known. Also, CPN does not have a counterpart among the human diseases associated with chronic renal failure.[56] The clinical implication of this LdT-associated increase in the incidence of nephropathy-related deaths among Sprague-Dawley rats is unclear.

In clinical studies with LdT, there was no evidence for nephropathy in the Phase 1 and 2 trials or the Phase 3 registrational trial. One Initial 15-Day IND Safety Report was submitted to both the LdT IND (IND 60, 459; Serial # 269) on August 29, 2006. In this report, Idenix reported that a 44 year-old male subject with diabetes mellitus, hypertension, hyperlipidemia, and pre-existing proteinuria developed nephrotic syndrome on Study Day 255 during study, NV-02C-004. NV-02C-004 is a randomized, blinded, phase 2b trial of LdT versus the combination of LdT and valtorcitabine (Val-LdC) in subjects with chronic hepatitis B. The subject was also taking cilazapril, metformin, gliclazide and simvastatin at the time of the adverse event. The Investigator assessed the relationship of study medication to the event as reasonably or possibly related to study drug. When unblinded, the subject was found to be on LdT (600mg) treatment arm.

The Applicant also conducted a search of the LdT SAE database for similar events using the following reported and verbatim terms: nephritic syndrome, proteinuria, diabetic nephropathy, diabetic kidney disease, nephritis, glomerular nephritis and nephropathy. One additional case of nephrotic syndrome was identified in a subject enrolled in NV-02B-019. This subject was ultimately unblinded and was not receiving LdT. A Medical Reviewer search of the clinical adverse event database for NV-02B-007 revealed five subjects (3 LdT; 2 LAM) with an AE of 'proteinuria' or 'protein urine present.' All four AEs were Grade 1-2 in severity and only one of these AEs required treatment. In addition, a search of the NV-02B-007 laboratory database for urinary protein abnormalities revealed:

Table 7.1.4A: NV-02B-007: Summary of New-Onset[57] Proteinuira by Baseline Toxicity.

Baseline/Screening Urine Protein → Higher Toxicity N (%)	**LdT** (680)	**LAM** (687)	**Total** (1367)
Neg/Trace→1+ proteinuria	33 (4.9)	37 (5.4)	70(5.1)
Neg/Trace→2+ proteinuria	7 (1.0)	1 (0.2)	8(0.6)
Neg/Trace→3+ proteinuria	0	1 (0.2)	1 (0)
1+ proteinuria →2+ proteinuria	2 (0.3)	1 (0.2)	3(0.2)
1+ proteinuria →3+ proteinuria	0	1 (0.2)	1 (0)
2+ proteinuria →3+ proteinuria	3 (0.4)	1 (0.2)	4 (0.3)
Total	45 (6.6)	42 (6.1)	87 (6.4)

Source: Medical Officer Review of LABS8 listings dataset, NV-02B-007

[56] Hard GC and Khan KN "A contemporary overview of chronic progressive nephropathy in the laboratory rat, and its significance for human risk assessment." Toxicologic Pathology 2004; 32:171-180.
[57] An urine protein elevation was considered to be "new-onset" if the on-treatment urine proteinuria finding was worse than baseline/screening.

Among these one LdT subject (#057-004) had a creatinine of 1.0 and 2+ proteinuria; his creatinine increased to 1.5 at week 40 and ranged between 1.1 and 1.6 through Week 84 and his proteinuria worsened to 3+ at Weeks 24 and 52. All other subjects on both treatment arms who developed with 2+ or 3+ proteinuria, however, did not have significant changes in their creatinine throughout the study.

MO Comments
The preclinical findings of increased CPN among male subjects on LdT have unclear significance. Analysis of the clinical adverse event and laboratory datasets for NV-02B-007 did not reveal evidence suggesting the development of nephropathy or other significant renal toxicity among subjects on LdT, relative to the LAM treatment group. The development of new-onset proteinuria was relatively similar between the treatment arms as shown in Table 7.1.4A. Based on current evidence, it seems unlikely that LdT worsens renal function in subjects with chronic hepatitis B and normal renal function. It is possible, however, that as more subjects with chronic hepatitis B and compromised renal function or at high risk for compromised renal function (e.g diabetes, hypertension, elderly, etc.) initiate treatment with LdT, an adverse event profile of nephropathy may emerge. It is hard to draw conclusions about the role of LdT based on the subject described in the IND safety report given his relatively high baseline risk for nephrotic syndrome and his underlying renal compromise.

Gastrointestinal
As noted above in Section 3.2, Animal Pharmacology/Toxicology, high LdT doses led to some gastrointestinal (GI) intolerance in pregnant rabbits, non-pregnant monkeys, and rats. The rabbits gained less weight; the monkeys had occasional soft stools and vomiting, whereas the rats had only occasional symptoms. In addition to reduced body weight gain and abnormal feces, one pregnant rabbit died at the 1000 mg/kg/day dose, two delivered prematurely and one aborted. These animals showed evidence of gastrointestinal irritation, including reduced food consumption and less body weight gain, abnormal feces, erosion on the stomach mucosal surface, reddish fluid and appearance in the intestine, and distended stomach and intestine (with gas). The death occurred after more than 10 doses of LdT administration; hence GI irritation appears to be a dose limiting toxicity in rabbits. The AUC value in the pregnant rabbits at 1000 mg/kg/day was 2-3 times higher than those at the highest doses studied in mice, rats, and monkeys, and 37 times higher than that in humans. Unlike the pregnant rabbits and the rats, the mice did not demonstrate GI intolerance.

One subject in the pivotal trial discontinued LdT due to an AE in the Gastrointestinal Disorders SOC. This subject (Subect # 005-007) was a 43 year old Asian male who developed nausea and loose stools after 389 days on study drug. This AE was ongoing with the subject eventually discontinuing LdT on Study Day 446. His GI symptoms resolving approximately 43 days after study drug discontinuation.

While approximately 30% of subjects in the pivotal clinical trial (NV-02B-007) experienced at least one adverse event (AE) in the Gastrointestinal Disorders System Organ Class (SOC), the rate of occurrence of these AEs was equal between the treatment arms (30% LdT and 30% LAM).

MO Comments
The preclinical GI toxicity is concerning at high LdT exposures, however, since the AUC associated with this GI toxicity is 37-times higher than that in humans, it is unlikely to be dose limiting in humans. Also, it is unusual to see such a late development of GI toxicity as in the subject who discontinued (Study Day 389). It is unknown, however, whether or not patients with pre-existing

gastrointestinal disease or patients who experience a significant LdT overdose may be at risk for a more serious GI toxicity.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The Safety population was to consist of all subjects who presumptively received at least one dose of the study medication with at least one observation after Baseline. Subjects who received study treatment other than the one randomly assigned were to be analyzed according to treatment received. For the analysis of AEs and other safety data, three treatment periods were defined:

On-Treatment Period

- Baseline to the date of last treatment + 7 days.[58]

Post-Treatment Period

- Safety-related follow-up period of the study, excluding the 7 days after the date of last treatment for subjects who discontinued from the study or who elected not to enter the follow-up study, NV-02B-022. Subjects who joined the follow-up study were not to have NV-02B-007 post-treatment data.

Off-Treatment Period

- Applicable only for subjects who discontinued treatment due to efficacy during the study. For subjects who do not experience post-treatment relapse, the off-treatment period is defined as 8 days after the date of last treatment through the subject's follow-up period. If the subject does not have a follow-up visit, the date of study discontinuation will be used. For subjects who experience a post-treatment relapse, the off-treatment period is 8 days after post-treatment discontinuation through the subject's date of restarting.

MO Comments

This integrated safety review focused on findings while subjects were receiving study drug, instead defining the on-treatment period as the time frame from study day 1 through 30 days off study drug. This definition enables capture of AEs that may have started shortly after study drug discontinuation, but outside of the 7-day window (11.2 half-lives). The pivotal study was ongoing at the time of database lock and very few subjects had discontinued study drug. Due to the difference in definition in "on-treatment" between this Medical Reviewer and the Applicant, there are slight differences in the numerical results generated in the AE analysis. The general trends found in this Medical Reviewer's AE analysis, however, support the Applicant's findings.

Adverse events were monitored throughout the pivotal study and reported in the CRF. Subjects were evaluated at the clinical site at Screening, Baseline, Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 52,

[58] For patients who discontinued treatment due to efficacy, if the patient resumes treatment due to post-treatment relapse, the On-Treatment period will also include the time from restarting blinded medication to 7 days after the patient's date of last treatment.

60, 68, 76, 84, 92, 100, and 104. Study subjects entering the follow-up period after discontinuation of treatment (for any reason) or completion of study treatment were evaluated every four weeks for four months after discontinuation of treatment. Adverse events considered by the investigator to be at least reasonably or possibly related to study drug and all serious adverse events are to be followed until they are resolved or assessed by the investigator to be chronic or stable. At each of these clinic visits adverse event and concurrent assessments were performed.

All adverse events recorded during the pivotal study include adverse events that the subject reports spontaneously, those observed by the investigator, and those elicited by the investigator in response to open-ended questions during scheduled study center visits.
Open-ended verbal questions included:
• "How are you feeling?"
• "Have you had any (other) medical problems since your last visit?"
• "Have you taken any new medicines, other than those provided to you in this study, since your last visit?"

All adverse events, regardless of relationship to study drug, were recorded on the Adverse Events CRF. All adverse event reports contained the following details regarding the adverse event: a brief description, onset date, duration, intensity/severity, treatment required, relationship to study drug, study drug action taken, outcome, and whether the event is classified as serious. Investigators were instructed to record severity of adverse events according to a modified version of the Division of AIDS Table for Grading Severity of Adult Adverse Events. For adverse events not included on the DAIDS Table, the investigator was instructed to determine the intensity of the adverse event according to the following criteria:

- Mild (Grade 1): Adverse event that disappears or is easily tolerated on continuation of study drug.
- Moderate (Grade 2): Adverse event sufficiently discomforting to cause interference with usual work activities.
- Severe (Grade 3): Adverse event that is incapacitating, with inability to work or perform daily activities.
- Life-Threatening (Grade 4): Adverse event that is *potentially* life-threatening.
    - If a life-threatening (Grade 4) adverse event is *immediately* life-threatening, the event was considered, by definition, serious and was reported to the [redacted] within 24 hours of the site's knowledge of the event.

AE and SAE information was collected from the time the subject consented to participate in the study until resolved or returned to baseline.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant categorized AEs using the MedDRA dictionary of System Organ Class and Preferred Terms. Adverse events were coded using the MedDRA dictionary version 6.1, except for NV-02B-003, for which adverse events were coded using the MedDRA dictionary 4.0. Cross-check of investigators' "verbatim" description of AEs compared to the designated MedDRA Preferred Term suggests that the Applicant's categorization of AEs was usually appropriate. In cases where this reviewer identified MedDRA preferred terms that were inappropriate or more clinically meaningful when grouped a different way the terms were regrouped and those changes

are reflected throughout the review.

7.1.5.3 Incidence of common adverse events

The safety review of the pivotal trial included data on 1367 nucleoside-naïve subjects (680 LdT subjects, 687 LAM subjects). The Applicant evaluated the rates of all AEs, AEs of Grade 2 to 4 intensity (moderate to life-threatening), AEs of Grade 3 and 4 intensity (severe to life-threatening), AEs identified as possibly, probably, or certainly related to study drug administration, and treatment-related AEs of Grades 2 to 4. These categories of AEs were compared across the treatment groups and for both the on-treatment and off-treatment periods. The rates of AEs reported in different categories were confirmed by the Medical Officers. Adverse events were reported frequently although there were few differences in the pattern of AEs reported by LdT-treated subjects compared to LAM-treated subjects.

The clinical AEs seen in this study were generally mild and transient. The majority of subjects experienced at least one AE between Baseline and Week 52. The incidence of AEs was similar in HBeAg-positive (74%) and HBeAg-negative (72%) subjects. Most AEs were reported as mild or moderate in intensity.

On-treatment AEs reported in > 2% of subjects in either arm in the studies included: headache, upper respiratory infection, nasopharyngitis, cough, pyrexia, abdominal pain, diarrhea, fatigue, arthralgia, dizziness, nausea, influenza, sore throat, rhinorrhea, dyspepsia, increased ALT, increased blood amylase, back pain, and myalgia.

Most of the reported events were mild and not considered related to study treatment. The proportions of subjects with reported AEs considered by the investigators to be possibly or probably related to blinded study drug were similar in the 2 treatment groups (LdT; LAM).

Reflective of the relatively small proportion of subjects who entered off-treatment follow-up, few subjects experienced AEs during the off-treatment period. There were no significant differences in the pattern of off-treatment AEs between the treatment groups.

7.1.5.4 Common adverse event tables

Adverse events were very common in the study populations. For this reason, the Applicant chose to present tables containing common AEs occurring in > 2% of subjects in any treatment arm. These events have been compiled and displayed below with a slightly higher cut-off rate of ≥ 2%.

Table 7.1.5.4 A: NV-02B-007: Most Common On-Treatment Adverse Events (Grades 1-4) Reported in ≥ 2% of Subjects in Either Treatment Arm of NV-02B-007, Without Regard to Causality

N (%)	LdT (n=680)	LAM (n=687)	Totals (n=1367)

All subjects with AE	508 (74.7)	485 (70.5)	993 (72.6)
Upper Respiratory Tract Infection	93 (13.7)	91 (13.2)	184 (13.5)
Fatigue/Malaise [a]	83 (12.2)	72 (10.5)	155 (11.3)
Nasopharyngitis	75 (11.0)	70 (10.2)	145 (10.6)
Headache [b]	73 (10.7)	97 (14.1)	170 (12.4)
Blood CPK increased	61 (9.0)	46 (6.7)	107 (7.8)
Abdominal Pain [c]	60 (8.8)	66 (9.6)	126 (9.2)
Cough	50 (7.4)	41 (6.0)	91 (6.7)
Influenza/Influenza-Like Symptoms[d]	48 (7.1)	55 (8.0)	103 (7.5)
Post-Procedural Pain	45 (6.6)	41 (6.0)	86 (6.3)
Nausea/Vomiting [e]	45 (6.6)	39 (5.7)	84 (6.1)
Diarrhea/Loose Stools [f]	44 (6.5)	34 (4.9)	78 (5.7)
Pharyngolaryngeal Pain	33 (4.9)	30 (4.4)	63 (4.6)
Pyrexia	29 (4.3)	19 (2.8)	48 (3.5)
Rash [g]	28 (4.1)	27 (3.9)	55 (4.0)
Arthralgia	28 (4.1)	26 (3.8)	54 (4.0)
Back Pain	27 (4.0)	25 (3.6)	52 (3.8)
Dizziness	25 (3.7)	33 (4.8)	58 (4.2)
Sensory Disturbances [h]	23 (3.4)	13(1.9)	36 (2.6)
Hepatic Pain/RUQ Pain [i]	19 (2.8)	26 (3.8)	45 (3.3)
Insomnia	19 (2.8)	15 (2.2)	34 (2.5)
Myalgia	19 (2.8)	14 (2.0)	33 (2.4)
Dyspepsia	17 (2.5)	36 (5.2)	53 (3.9)
ALT increased	16 (2.4)	18 (2.6)	34 (2.5)
Pruritus [j]	16 (2.4)	18 (2.6)	34 (2.5)
Anorexia/Decreased Appetite [k]	15 (2.2)	11 (1.6)	26 (1.9)
Gastritis	15 (2.2)	6 (0.9)	21 (1.5)
Rhinorrhea	14 (2.1)	19 (2.8)	33 (2.4)
Asthenia	14 (2.1)	10 (1.5)	24 (1.8)
Acne [l]	13 (1.9)	11 (1.6)	24 (1.8)
Hypertension	12 (1.8)	11 (1.6)	23 (1.7)
Toothache	12 (1.8)	11 (1.6)	23 (1.7)
Rhinitis	12 (1.8)	10 (1.5)	22 (1.6
Abdominal Distention	11 (1.6)	13 (1.9)	24 (1.8)
Urinary Tract Infection	11 (1.6)	3 (0.4)	14 (1.0)

Source: Medical Officers Review of electronic listings and analysis datasets AE and AAE for NV-02B-007.

[a] Includes preferred terms: fatigue and malaise

[b] Includes preferred terms: headache, migraine, sinus headache, and tension headache

[c] Includes preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain. Adverse events under preferred term "abdominal pain upper" with an event or lower level term descriptions of right upper quadrant pain were excluded from the abdominal pain category and coded under hepatic pain/RUQ pain.

[d] Includes preferred terms: influenza and influenza-like symptoms

[e] Includes preferred terms: nausea, vomiting and retching

[f] Includes preferred terms: diarrhea, loose stools, and frequent bowel movements

[g] Includes preferred terms: rash, rash erythematous, rash macular, rash maculo-papular, rash scaly and rash papular. Adverse events under preferred term "rash papular" with an event or lower level term description of pimples on the face were excluded from the rash category and coded under acne.

[h] Includes preferred terms: dysesthesia, dysgeusia, sensory loss, intercostal neuralgia, neuropathic pain, polyneuropathy, sciatica, sensation of heaviness, paraesthesia, hypoaesthesia, hypoaesthesia oral, paraesthesia

oral, and neuralgia
[i] Includes preferred terms: hepatic pain, abdominal pain upper with event or lower level term descriptions of right upper quadrant pain.
[j] Includes preferred terms: pruritus and pruritus generalized.
[k] Includes preferred terms: anorexia and decreased appetite.
[l] Includes preferred terms: acne, acne cystic, acne pustular, and rash papular (with event or lower level term description of pimples on the face).

The Applicant also tabulated the AEs that were considered treatment related and of Grade 2 to 4 severity (moderate to life threatening). These events represent those that are more likely to be related to study drug and require intervention, either another type of treatment or interrupting or discontinuing the study treatment. Events of this severity were relatively uncommon across study treatments. This type of tabulation as shown in Table 7.1.5.4B is generally considered appropriate for inclusion in the product label for a new drug.

Table 7.1.5.4B: NV-02B-007: Selected Clinical Adverse Events[a] (Grade 2-4) of Moderate to Severe Intensity

Body System/Adverse Event	LdT 600 mg (n=680)	LAM 100 mg (n=687)
All subjects with any Grade 2-4 AE	150 (22.1%)	153 (22.3%)
General		
Fatigue/Malaise [b]	8 (1.2%)	9 (1.3%)
Pyrexia	8 (1.2%)	2 (0.3%)
Musculoskeletal & Connective Tissue		
Arthralgia	6 (0.9%)	7 (1.0%)
Muscle-Related Symptoms [c]	11 (1.6%)	10 (1.5%)
Gastrointestinal		
Abdominal Pain [d]	7 (1.0%)	3 (0.4%)
Diarrhea/Loose Stools [e]	5 (0.7%)	2 (0.3%)
Gastritis	5 (0.7%)	0
Respiratory, Thoracic, & Mediastinal		
Cough	5 (0.7%)	5 (0.7%)
Nervous System		
Headache [f]	9 (1.3%)	16 (2.3%)

[a] Includes adverse events categorized as possibly/reasonably or not possibly/reasonably related to the treatment regimen by the Investigator. Excludes upper respiratory infection, pharyngitis/nasopharyngitis, post-procedural pain, influenza and influenza-like symptoms and laboratory abnormalities that were considered Adverse Events. Please see Section 7.1.7 for a discussion of laboratory abnormalities. Also Excludes events with a frequency of less than 0.7% in the LdT treatment group.
[b] Includes preferred terms: fatigue and malaise
[c] Includes preferred terms: back pain, fibromyalgia, muscle cramp, musculoskeletal chest pain, myalgia, myopathy, pain, pain in extremity, and tenderness. See further discussion of myopathy under Section 7.1.3.3: Other significant adverse events.
[d] Includes preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and gastrointestinal pain. Adverse events under preferred term "abdominal pain upper" with an event or lower level term descriptions of right upper quadrant pain were excluded from the abdominal pain category

and coded under hepatic pain/RUQ pain.
[e] Includes preferred terms: diarrhea, loose stools, and frequent bowel movements
[f] Includes preferred terms: headache, migraine, sinus headache, and tension headache

Based upon review of the adverse events in the pooled studies, NV-02B-007 and NV-02B-015, provided with the Clinical Summary Document for the 120-Day Safety Update, the safety profile, overall, was not substantially different from that seen in the first year of treatment in the pivotal NV-02B-007 study.

7.1.5.5 Identifying common and drug-related adverse events

None of the Phase 2 or Phase 3 studies of sufficient length to identify AEs were placebo-controlled, so it is possible that drug-related adverse events occurred but were not detected because they occurred at the same rate as seen in the active control LAM groups. While the differences were not large, there seems to be a consistently higher frequency[59] of on-treatment fatigue/malaise, diarrhea/loose stools, and pyrexia in the LdT arm, when compared to the LAM arm. Based on what is known of the nucleoside analogue class and the preclinical findings (gastrointestinal intolerance), LdT can reasonably be considered the cause of these and other adverse events commonly observed in the Phase 1 through Phase 3 clinical trials. Also notable, was the less frequent occurrence of on-treatment headaches, dyspepsia, and ALT elevations/ALT flares among LdT subjects when contrasted with LAM subjects (see Table 7.1.5.4 A).

In addition, based on the data reviewed, the elevated creatine kinase levels appear to be LdT-specific, above and beyond what is expected for this drug class. There was not a difference between the LdT treatment arm and the LAM control arm for the development of myalgias and other muscle-related adverse events (ref) among all subjects and within the subset of subjects that developed CK elevations. There were, however, a greater proportion of subjects on LdT than the comparator arm, with adverse events associated with muscular weakness. Four of these LdT subjects had myopathies, two of which were SAEs, and three of which ultimately resulted in study drug discontinuation. There seems to be reasonable evidence to suggest that LdT may play a causal role in the development of this toxic myopathy.

7.1.5.6 Additional analyses and explorations

The Applicant provided additional subgroup analyses for the demographic (age, gender, race) and disease characteristic (route of HBV transmission, HBeAg status, Baseline ALT) to evaluate AEs in the pivotal NV-02B-007 study. In general, these factors did not markedly affect the overall pattern or rate of AEs seen. The following observations were made:

- AEs were proportionally higher with increasing age, among women, and in "Other" ethnic groups compared to Caucasians and Asians. These subject groups were small relative to other demographic groups, which could result in unreliable estimates for these groups.
- Prior to Week 24 ALT flares were more common in HBeAg-positive subjects than in HBeAg-negative subjects

[59] Adverse events with a difference of 1.5% or greater between the treatment arms were included here

The AE data were analyzed by HBeAg-positive status and HBeAg-negative status based on Screening results. The overall incidence of AEs was similar in HBeAg-positive (74%) and HBeAg-negative (72%) subjects. SAEs were slightly more frequent, overall, in HBeAg-negative subjects. The patterns of specific AEs and SAEs, by treatment, for the two HBeAg populations were similar to those observed in the overall population.

The Applicant also analyzed AEs by age group, gender, and ethnicity. In general, the incidence of AEs was higher with increasing age, and among women. AEs also appeared to occur at much higher rates in groups other than Asians and Caucasians, but this may reflect the fact that the number of subjects in ethnic groups other than Asians and Caucasians was low (118/1367).

Overall, similar proportions of White and Asian subjects experienced an AE during the NV-02B-007 study. The Applicant identified minor differences, however, in clinical AEs based on race. In this analysis, the only subgroups with adequate numbers to evaluate were Asians and Whites. Among, LdT-treated subjects, Asians had higher rates of the following on-treatment adverse events: upper respiratory infection (17% versus 1%); nasopharyngitis (12.6% versus 6.1%); cough (8.0% versus 3.1%); influenza/influenza-like symptoms (7.2% versus 5.1%); dizziness (4.0% versus 2.0%); back pain (3.8% versus 2.0%); dyspepsia (3.0% versus 1.0%); and gastritis (2.7% versus 1.0%).

Also, among LdT-treated subjects, Whites had higher rates of the following on-treatment adverse events: fatigue/malaise (15.3% versus 11.8%); headache (19.4% versus 8.6%); increased CPK (12.2% versus 7.2%); arthralgia (11.2% versus 3.2%); ALT increased (4.1% versus 2.3%); asthenia (3.1% versus 1.5%); rhinitis (3.1% versus 1.5%); hypertension (3.1% versus 1.0%); peripheral edema (3.1% versus 0.2%); and contusion (2.0% versus 0%). SAEs were slightly more frequent overall in the Causcasian and Other categories, but no patterns of predominant SAEs were evident. Among LdT-treated subjects, there were no significant differences between the racial groups in terms of SAEs (Asians: 15 (3.5%); Caucasians: 5 (4.5%)). The Applicant notes that similar clinical differences across racial groups were also observed in subjects receiving LAM.

Overall, 46 (6.2%) Asians and 13 (4.4%) Caucasians experienced SAEs, a less than two percent difference between the racial groups. Similarly, among LAM-treated subjects, less than two percent fewer Caucasians, when compared to Asians, experienced SAEs. Of note, SAEs were slightly more frequent overall in HBeAg-negative subjects, but no pattern of predominant SAEs was evident.

MO Comments
Although Caucasians and Others had higher overall rates of SAEs than Asians, the pattern of difference may reflect the differences in sample sizes between the groups or cultural differences. Some individual differences by preferred term or system organ class were evident within the ethnic subsets, but because the numbers of subjects in the Caucasian and Other categories are relatively small as compared to the Asian group, it is not clear if the differences might be the effect of a small sample size. There were not adequate numbers of blacks/African Americans, Hispanics, and other minority groups enrolled in the clinical development program to be assured that the safety profile in this subgroup is similar to those of other racial groups. In particular, the proportion of African-Americans in the clinical trial significantly under-represents this group compared to an increased prevalence of chronic HBV in African Americans in the U.S. population.

Minor differences in clinical AEs and laboratory abnormalities were identified based on gender. Overall, a higher proportion of female subjects reported AEs (75.8% versus 72.8%) during the NV-02B-007 study. When examined by treatment group, however, the difference between the genders

was slightly more prominent among LAM-treated subjects (74.7% versus 70.5%) than among LdT-treated subjects (76.9% versus 75.1%). Female subjects receiving LdT had a higher rate of reported fatigue/malaise (15.0% versus 11.6%); headache (15.0% versus 11.6%); influenza/influenza-like symptoms (9.2% versus 6.3%); acne (5.8% versus 0.6%); rash (5.8% versus 3.6%); and asthenia (4.0% versus 1.4%). Male subjects receiving LdT reported very few clinical adverse events at higher rates than female subjects, except elevated CK (10.5% versus 4.6%), when reported as a clinical AE. Similar gender differences were observed in the LAM-treated subjects, with more remarkable differences between male and female subjects noted for nausea/vomiting (11.4% versus 4.2%); dizziness (10.8% versus 3.0%); cough (8.2% versus 5.5%); arthralgia (5.7% versus 3.4%); and hepatic/RUQ pain (5.7% versus 3.8%). As noted for LdT-treated subjects, male LAM subjects had a higher rate of increased CK, reported as an AE, than female subjects (7.6% versus 3.8%).

When examined by gender, there were differences in some laboratory abnormalities between the treatment arms. Female subjects on LdT had a higher rate of Grade 3-4 CK abnormalities, when compared to male subjects on LdT (13.9% versus 10.1%), yet a notably higher proportion of male subjects on LdT had Grade 1-4 CK abnormalities than female subjects on LdT (80.3% versus 46.8%). Among LAM-treated subjects, there was no gender difference for Grade 3-4 CK abnormalities, but more male subjects had Grade 1-4 CK abnormalities than female subject (46.5% versus 25.9%).

MO Comments
There is individual and population variation in serum CK levels. High levels of CK have been seen in healthy males compared with healthy females and in those with large muscle mass. This might contribute to the higher prevalence of CK elevations (Grade 1-4) among male subjects, but does not explain the higher proportion of Grade 3-4 CK abnormalities among female subjects.

Minor differences in clinical AEs and laboratory abnormalities were also identified based on age. Subjects with age 16 $\leq$ age $\leq$ 20 made up 8.4% of the study population; and subjects with age $\geq$ 60 made up 3.2% of the study population. In spite of small numbers, it appeared that subjects with age > 60 had a slighter higher rate of clinical AEs overall (82% versus 63% for those subjects age < 20). The subjects with age $\geq$ 60 had more AEs including arthralgia, increased CPK, increased amylase and/or lipase, ALT, influenza/influenza-like symptoms, and hypertension. Subjects between the ages of 16 and 20 had higher rates of nasopharyngitis, upper respiratory tract infection, diarrhea/loose stools, anorexia/decreased appetite, and toothaches, when compared to subjects 21-59 years of age.

It appeared that subjects $\geq$ 60 years of age had a higher rate of Grade 3-4 CK abnormalities (15.8% versus 11% for subjects aged 16-20 and 8.5% for subjects aged 21-59) in the LdT treatment arm only. For LAM-treated subjects, there were no Grade 3-4 CK abnormalities among subjects $\geq$ 60 years of age versus 5.4% for subjects aged 16-20 and 8.5% for subjects aged 21-59.

MO Comment
Differences in clinical AEs and laboratory abnormalities based on age were consistent with the expected longer duration of illness in older subjects and changes related to aging. The age-related differences in CK abnormalities seen between the LdT and LAM treatment arms are likely related to the higher prevalence of CK abnormalities among LdT recipients. The higher rate of Grade 3-4 CK abnormalities among the very young (age 16-20) and older (age $\geq$60) LdT subjects is concerning.

Exploratory analyses were also undertaken to assess the relationships between ALT flares[60], HBV DNA levels, viral breakthrough, and other parameters. It was found that Grade 3-4 ALT flares during the first 24 weeks were more common in subjects with HBV DNA reductions greater than 4 log10 copies/mL from Baseline at Weeks 12 and 24. Per the Applicant's analysis, most subjects with Grade 3-4 ALT flares had failed to achieve undetectable HBV DNA levels (94.1%) or HBeAg loss (88.2%) at Week 52.

Logistic regression analyses suggest that Virologic Breakthrough, LAM treatment (as compared with LdT treatment) and lower ALT at Baseline were associated with an increased risk of Grade 3-4 ALT flares between Weeks 24 and 52. ALT randomization strata (ALT < 2.5 versus ≥ 2.5 ULN) and HBeAg status randomization strata (HBeAg-negative versus HBeAG-positive), and gender were not found to be associated with an increased risk of Grade 3-4 ALT flares. Since ALT flares were often associated with viral breakthrough and/or evidence of treatment failure, the flares sometimes resulted in study discontinuation (see section 7.1.3.2, Adverse Events Associated with Dropouts).

MO Comments
Please see Section 7.1.3.3 for a more detailed discussion of ALT Flares.

Subgroup analyses were not performed for NV-02B-003 and NV-02B-010, either because they were not applicable (e.g. NV-02B-003 enrolled only HBeAg-positive subjects) or the sample size was too small to draw any meaningful conclusions.

Based on the 120-Day Safety Update, the Applicant notes that the observations regarding age, gender, and race made during the first year of the pivotal study were similar to those seen in the pooled dataset (NV-02B-007/NV-02B-015) and in the second year of the pivotal study, NV-02B-007. Overall, fewer AEs were reported in the second year of treatment.

7.1.6 Less Common Adverse Events

Less common AEs (< 1%) were identified in the safety database but the number of subjects in the database was not adequate to conduct a formal analysis across treatment groups for events occurring at low frequency.

The occurrence of myopathy among subjects on LdT, which qualifies as a less common, but concerning adverse event, was discussed in further detail in Section 7.1.3.3: Other Significant Adverse Events.

7.1.7 Laboratory Findings

Evaluation of clinical laboratory parameters was conducted by analyzing the proportion of subjects in each treatment group who experienced marked laboratory abnormalities during the pivotal study.

[60] The statistical analysis plan for NV-02B-007 described four categories of ALT flare, used by the sponsor in their initial analysis: (1) ALT Flare Category 1: ALT elevation ≥ 2× Baseline (and ≥ 2× ULN); (2) ALT Flare Category 2: ALT elevation ≥ 3× Baseline (and ≥ 3× ULN); (3) ALT Flare Category 3: ALT elevation ≥ 500 IU/L and ≥ 2× Baseline; and (4) ALT Flare Category 4: ALT elevation ≥ 2× Baseline with bilirubin ≥ 2× Baseline (and ≥ 2× ULN).

Marked laboratory abnormalities were identified using a standardized DAIDS toxicity grading table. The applicant evaluated laboratory abnormalities according to three treatment periods: on-treatment, post-treatment, and off-treatment periods as specified in the NV-02B-007 Statistical Analysis Plan. The treatment periods are defined:

On-Treatment Period

- Baseline to the date of last treatment + 7 days.[61]

Post-Treatment Period

- Safety-related follow-up period of the study, excluding the 7 days after the date of last treatment.

Off-Treatment Period

- Applicable only for subjects who discontinued treatment due to efficacy during the study. For subjects who do not experience post-treatment relapse, the off-treatment period is defined as 8 days after the date of last treatment through the subject's follow-up period. If the subject does not have a follow-up visit, the date of study discontinuation will be used. For subjects who experience a post-treatment relapse, the off-treatment period is 8 days after post-treatment discontinuation through the subject's date of restarting.

This integrated safety review focuses on treatment-emergent/on-treatment laboratory findings, using the treatment period defined above. In addition to evaluating marked laboratory abnormalities, the Medical Officer also assessed mean changes from baseline for selected laboratory tests.

7.1.7.1 Overview of laboratory testing in the development program

As per the NV-02B-007 protocols, blood samples for hematologic and chemistry safety laboratory analyses[62] were collected at baseline and all subsequent visits (Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 68, 76, 84, 92, 100, and 104. Serum HBV DNA levels were also obtained at each of these study visits. Urine samples were collected at screening, baseline and Weeks 24, 52, and 104.[63] Serum for HBeAg, antibody to HBeAg (HBeAb), HBsAg, and antibody to HBsAg (HBsAb) werl be obtained at Screening, Baseline, Weeks 12, 24, 32, 40, 48, 52, 60, 68, 76, 84, 92, 100, 104, premature study discontinuation, and at all follow up visits (Weeks 108, 112, 116, 120). Prothrombin time was to be measured pre-treatment (screening and baseline) and at Weeks 52 and 104 (or final on-study visit).

A serum pregnancy test (beta-human chorionic gonadotropin, β-HCG) was obtained at the screening visit in females of childbearing potential. Subsequent urine pregnancy tests were

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[61] For patients who discontinued treatment due to efficacy, if the patient resumes treatment due to post-treatment relapse, the On-Treatment period will also include the time from restarting blinded medication to 7 days after the patient's date of last treatment.

[62] The following laboratory parameters were measured: (1)**Hematology:** hemoglobin (Hgb), hematocrit (Hct), platelets, white blood cell count (WBC), absolute neutrophil count (ANC); (2) **Serum Chemistries:** creatinine (Cr), total protein (TP), amylase, lipase, creatine phosphokinase (CPK) (also know as creatine kinase (CK)), alphafetoprotein(AFP); (3) **Serum Liver Function Tests:** alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (Alb), total bilirubin (TB); and (4)**Coagulation:** prothrombin time (PT).

[63] Urinalysis testing included only specific gravity, pH, protein, and glucose.

performed at Weeks 52 and 104 (or final on-study visit) and at any interim study visit, if suggested by the subject's interval history.[64] Serologic testing for HIV-1 and HIV-2, HCV, HDV, and AFP were also performed at the Screening visit.

Laboratory abnormalities of clinical significance, as determined by the investigator were reported as AEs or SAEs if they were detected after study drug administration or present at baseline and worsened after study drug administration.

Grade 3 or 4 laboratory abnormalities, judged to represent a clinically significant adverse change by the Investigator, were eligible for repeat testing (via the central lab). Abnormal values were followed until they returned to baseline, or an adequate explanation was to be given if the abnormal values become stable.

The Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experience was adapted and used to assess the severity of laboratory test abnormalities. Adaptations were limited to liver function tests (AST, ALT, alkaline phosphatase).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory datasets were available for the LdT Phase 2 and 3 development program. The laboratory data reviewed for this Clinical Review focused on that from the pivotal trial, NV-02B-007, where the rates of laboratory abnormalities on the LdT arm were analyzed and compared to the rates of laboratory abnormalities on the LAM arm.

7.1.7.3 Standard analyses and explorations of laboratory data

The Applicant and the FDA analyzed laboratory test results for all subjects in the NV-02B-007 trial who had both a baseline and an on-treatment or final laboratory measurement. The vast majority of subjects on both arms of the NV-02B-007 trial met this criterion. There were slightly more missing values for laboratory tests such as PT, INR, and urinalysis compared to routine serum chemistry and hematology studies. The following Table presents new-onset, on-treatment (treatment-emergent) laboratory values occurring in > 2% of subjects.

Table 7.1.7.3.1b: NV-02B-007: Treatment-Emergent Laboratory Abnormalities Reported in ≥ 2% of Subjects on LdT

	Limit	**LdT** (n=680)	**LAM** (n=687)
Hematology			
WBC	$\leq 2.9 \times 10^9$ /L	18 (2.6%)	20 (2.9%)
Neutropenia	ANC < 1500/mm^3	66 (9.7%)	83 (12.1%)
Thrombocytopenia			

[64] In France only, females of childbearing potential had urine pregnancy tests regardless of patient's interval history at the following visits: Week 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 68, 76, 84, 92, 100, and 104 and subsequent urine pregnancy test at any other interim study visit if suggested by the patient's interval history

Grade 1	Platelets: 70,000-99000/mm^3	29 (4.3%)	24 (3.5%)
Grade 2	Platelets: 50,000-69,999/mm^3	11 (1.6%)	7 (1.0%)
Prothrobmin Time			
Grade 1	≥ 1.0- 1.25 x ULN	18 (2.8%)	24 (3.8%)
Grade 2	> 1.25 – 1.5 x ULN	3 (0.5%)	4 (0.6%)
Chemistry			
Amylase			
Grade 1-2	1.0 x ULN ≤ amylase ≤ 3.0 x ULN	126 (18.5%)	145 (21.1%)
Lipase			
Grade 1-2	1.0 x ULN ≤ lipase ≤ 2.5 x ULN	101 (14.9%)	115 (16.7%)
Grade 3-4	> 2.5 x ULN	12 (1.8%)	25 (3.6%)
ALT			
Grade 1	1.1-2.0 x baseline	217(31.9%)	195(28.4%)
Grade 2	>2.0-3.0 x baseline	49(7.2%)	50(7.3%)
Grade 3	> 3.0 x baseline	27(4.0)	51(7.4%)
Grade 4	>10 x baseline and/or evidence of hepatic failure	1(0.2%)	2(0.3%)
AST			
Grade 1	1.1-2.0 x baseline	241(35.4%)	214(31.1%)
Grade 2	>2.0-3.0 x baseline	53(7.8%)	37(5.4%)
Grade 3	> 3.0 x baseline	23(3.4%)	38(5.5%)
Grade 4	>10 x baseline	0	1(0.2%)
Creatinine			
Grade 1	≥ 1.0 – 1.5 x ULN	33(4.8%)	22(3.2%)

Source: Medical Officer Review of electronic dataset LABBYPT3 for NV-02B-007.

MO Comments

*The FDA analysis confirms the Applicant's findings of treatment-emergent laboratory abnormalities. Neutropenia (*ANC < 1500/mm^3*), amylase, lipase, and Grade 3-4 ALT and AST elevations occurred more frequently in LAM recipients, while CK elevations, Grade 1 creatinine and Grade 1-2 ALT/ AST elevations were more frequent in LdT recipients. Please see Section 7.1.3.3 for a more detailed discussion of CK elevations and ALT flares. Absolute neutrophil counts and platelet counts were assessed routinely and instances of neutropenia and thrombocytopenia were reported by the central laboratory. The Applicant argues that sporadic shipping-related artifacts account for the instances of neutropenia and thrombocytopenia that were reported by the central laboratory and not confirmed by the local laboratory, but this does not explain the majority of ANC and platelet abnormalities. Please see Section 7.1.7.3.2 for a more detailed discussion of*

ANC and platelet abnormalities.

In the context of CK elevations, elevations of serum creatinine would usually be concerning. The limited severity of creatinine elevations and the Medical Reviewer subanalysis of creatinine vaules among subjects with musculoskeletal symptoms within 2 months of a CK elevation (median creatinine of 0.9) suggest that rhabdomyolysis with concurrent renal failure did not occur among subjects in NV-02B-007. For further discussion of this analysis, see Section 7.1.3.3, Other Significant Adverse Events.

7.1.7.3.1 Analyses focused on measures of central tendency

The Applicant did provide an analysis of mean or median changes from baseline in laboratory values for hematologic and chemistry parameters. The Medical Officer also conducted this type of analysis for selected laboratory parameters, primarily those related to liver function.

For most of the laboratory parameters evaluated, there were insignificant changes over the first 52 weeks of study drug dosing. Abnormal ALT consistent with active HBV was one of the entry criteria for the Phase 3 study. As might be expected for a drug like LdT with activity against HBV, serum ALT decreased from baseline to Week 52 and beyond in the both groups of subjects receiving LdT or LAM. Subjects receiving LAM experienced a similar decrease in mean ALT from baseline to Week 52 and beyond.

Table 7.1.7.3.1A: NV-02B-007: Change from Baseline for Selected Laboratory Tests

		LdT			LAM	
Chemistry	**N**	**Median Baseline Values**	**Median Change at Week 52**	**N**	**Median Baseline Value**	**Median Change at Week 52**
ALT (U/L)	680	106.5	-72	687	108	-71
AST (U/L)	680	62	-28	687	59	-31
Total Bilirubin (mg/dL)	680	0.7	0	687	0.7	0
Creatinine (mg/dL)	680	0.9	-0.05	687	0.9	0
CK	680	104.5	69	687	103	8

Amylase	680	82	-2.0	687	81	-2
Lipase	680	34	-2.0	687	34	0
Hematology						
WBC	680	5.5	0.2	687	5.5	0.2
ANC	680	3.04	0.325	687	2.9	0.2
Hemoglobin	680	15	0	687	15.1	0.1
Hematocrit	680	45	0.2	687	45	0.6
PT	680	12.0	0	687	12.0	0.10
Platelets	680	189	18.0	687	186	15.0

Source: Medical Officer Review of electronic analysis dataset, LABBYPT2, for NV-02B-007.

MO Comments
When looking at labs in terms of change from baseline once again a difference between study arms is noted for creatinine kinase. There is a noticeable difference in CK with the LdT arm having CK increase by a median of 69, while the LAM arm had a median increase of 8. See Section 7.1.3.3 for a more detailed discussion of CK elevations in the study. Although there were greater proportions of subjects with ALT elevations on the LAM arm, when compared to the LdT arm, this difference is not reflected in the ALT change from baseline. For ALT, the median change from baseline was similar between both study arms and reflects the expected decrease in ALT associated with treatment for chronic hepatitis B. Also, the median changes from baseline for ANC and platelet counts were minimal, similar between both study arms, and not of clinical significance.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The primary laboratory safety analysis presented by the applicant evaluated the proportion of subjects in each treatment group who developed markedly abnormal values in the Phase 3 pivotal study. As noted above, the applicant utilized a laboratory toxicity grading system adapted from Division of AIDS Table for Grading Severity of Adult Adverse Experiences. This toxicity grading system was considered acceptable for use in clinical trials. Laboratory abnormalities were evaluated in terms of occurrence of any toxicity grade (Grades 1 to 4) or occurrence of marked abnormalities (Grades 3 or 4). Laboratory abnormalities that were considered clinically significant by the investigator were also reported as AEs and have been included in the discussion of those events in Section 7.1.5.4, Common adverse events.

The most commonly observed hematologic or coagulation abnormalities were decreased ANC, decreased platelets, and prolonged PT. In NV-02B-007, 66 (9.7%) LdT subjects compared to 83 (12.1%) LAM subjects had neutropenia (ANC < 1500/mm^3) on-treatment. Grade 3 or 4 ANC abnormalities occurred less frequently in 13 (1.9%) subjects on LdT and 11 (1.6%) subjects on LAM. Also, in this population 45 (6.6%) LdT subjects compared to 34 (4.9%) LAM subjects had low platelet counts at some time on-treatment but Grade 3 or 4 platelet abnormalities were unusual. During the on-treatment period, prolonged PT was observed in 21 (3.1%) of LdT subjects and 28 (4.1%) of LAM subjects. However, Grade 3 or 4 abnormalities of PT were not observed in either arm. Abnormalities in other hematologic parameters were infrequent and balanced across treatment groups.

There were few significant abnormalities in serum biochemical tests. While Grade 3-4 elevations of pancreatic enzymes occurred infrequently, Grade 1-2 elevations were more common as shown in Table 7.1.7.3.1. All elevations of pancreatic enzymes, however, were more common among LAM

recipients. The most commonly observed biochemical abnormalities were elevations in creatine kinase and liver transaminases. In general, mean ALT and AST levels decreased among the treatment groups in both treatment arms as noted above, but ALT flares did occur and were more common on the LAM study arm.

A representative sample of subjects with Grade 3 or 4 laboratory abnormalities that have worsened from baseline is displayed in Table 7.1.7.3.2A. For many laboratory tests, no or very few subjects in the Phase 3 studies experienced a laboratory abnormality > Grade 3. For example, no subjects had a Grade 2-4 elevation in creatinine throughout the study. All INRs and WBCs remained within normal range.

Table 7.1.7.3.2A: NV-02B-007: Subjects Increasing from Baseline to Grade 3 or Grade 4 Toxicity On Treatment

Laboratory Parameter	**HbeAg-negative**		**HBeAg-positive**	
	LdT (n=235)	**LAM (n=232)**	**LdT (n=445)**	**LAM (n=455)**
Absolute neutrophil count	8	2	5	9
ALT	2	12	26	41
Amylase	1	2	0	0
AST	4	10	19	29
Lipase	8	14	4	11
Platelets	2	1	3	2
Total bilirubin	0	0	0	2
Creatine Kinase	20	8	41	14

Source: Medical Reviewer analysis of the electronic analysis dataset, LABBYPT3, for NV-02B-007.

MO Comments
The method of searching for significant worsening of a laboratory value from baseline to a Grade 3 or 4 toxicity level essentially "corrects" for those subjects who had markedly abnormal values at study entry and then improved over time. It does not account for subjects who may have improved and then worsened again (e.g., a subject who started at Grade 3 ALT, improved to Grade 1 toxicity level, then worsened to Grade 3 later). A representative sample of laboratory values displayed in this way is shown above in Table 7.1.7.3.2A and will likely be displayed in the product label.

Based upon the Clinical Summary Document provided with the 120-Day Safety Update, new-onset Grade 3-4 hematologic abnormalities occurring during the first 52 weeks of treatment for the pooled studies, NV-02B-007 and NV-02B-015, consisted of decreases in absolute neutrophil count (ANC), and changes in prothrombin time (PT) and platelet counts. Two subjects on LdT versus zero subjects on LAM developed Grade 3-4 abnormalities in prothrombin time in this analysis. In general, however, the frequency of these abnormalities was similar across treatment groups. Longer term data (post Week 52 to Week 104) from NV-02B-007 show similar Grade 3-4 abnormalities in ANC and platelet counts by treatment group. In NV-02B-011, in addition to Grade 3-4 ANC decreases (9 subjects; 8.6%), platelet count decreases (15 subjects; 14.3%), Grade 3-4 hemoglobin decreases (1 subject, 1.0%) and PT increases (10 subjects; 9.5%) were also reported. The Grade 3-4 chemistry findings provided in the120-Day Safety Update appeared similar to those already seen in the original NDA submission. Information on ALT flares and CK elevations provided with the 120-Day Safety Update are discussed separately in Section 7.1.3.3, Other Significant Adverse Events.

MO Comments
While Grade 1 and 2 abnormalities in prothrombin time were seen in the original NDA submission, Grade 3-4 abnormalities were noted only when the NV-02B-007 data were pooled with NV-02B-015. Based on the data in Table 7.1.7.3.1, slightly more subjects on LAM developed Grade 1-2 abnormalities in prothrombin time, when compared to subjects on LdT. The occurrence of Grade 3-4 abnormalities in PT in 2 subjects on LdT is notable, but may not reflect a true increase in risk relative to LAM, given the small numbers under consideration.

The laboratory data reported in the 120-Day Safety Update for the still-blinded subjects in the ongoing study, NV-02B-011, are not unexpected in a decompensated population.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Individual study subjects who developed laboratory abnormalities that were considered clinically significant were reported as AEs. Subjects who discontinued study drug because of marked laboratory abnormalities were included in the discussion of AEs resulting in study drug discontinuation presented in Section 7.1.3.2.

7.1.7.4 Additional analyses and explorations

There are limited data available for LdT doses other than 600 mg once daily. In NV-02B-001, the Phase 1 dose-finding study, a range of doses between 25 mg once daily and 800 mg once daily for 28 days did not demonstrate any dose-related or dose-limiting toxicities, or a specific pattern of AEs related to dose. Likewise, LdT 1800 mg once daily for 5 days was studied in NV-02B-024 and was well tolerated with no dose-related or dose-limiting toxicities. The AE profile did not differ appreciably from that of LdT 600 mg once daily for 2 weeks in the same study.

Although the number of subjects in the treatment groups in NV-02B-003 was small, there was no discernible pattern of AEs to suggest that the AE profile of LdT 400 mg once daily and LdT 600 mg once daily for up to one year had any appreciable differences in safety profile with regard to the system organ classes affected, frequency of any specific AEs, relationship to study drug, or severity of AEs.

Based on information provided in the 120-Day Safety Update, there was very little difference in the types of AEs or percentages of subjects reporting AEs from Baseline to Week 76 compared to the first year of treatment, with the exception of CK elevations. Within the first 76 weeks of study treatment, CK elevations were reported in proportionally more LdT-treated subjects than LAM-treated subjects, similar to the results of analysis of the data available at the time of database lock for the original NDA submission. There were fewer AEs reported overall during the second year of treatment (21.4%) than the first year (70.9%), but this may be a reflection of the decreasing number of subjects with available data over the second year.

Data collected in the third year (nominal Week 104 to nominal Week 156 or last study visit) of the NV-02B-010 study were available at the time of the 120-Day Safety Update and showed that more subjects in the LdT treatment groups reported an AE than LAM monotherapy subjects. Similar proportions of subjects in LAM and LdT monotherapy groups had increased ALT; a higher

percentage of subjects on combination therapy experienced flu than those receiving monotherapy. In general, frequencies were low, but subject numbers were small in each treatment group and the denominator has not been adjusted for discontinuations over time. Fewer subjects reported AEs in the third year of treatment than in the previous years, however, there were fewer subjects contributing to data during that period.

7.1.7.5 Special assessments

Assessment of hepatotoxicity, considered a special laboratory assessment for reviews of other drugs is an integral part of both the efficacy and safety evaluation of any drug for chronic HBV. For an evaluation of potential hepatotoxicity, refer to the discussion of ALT flares presented in Section 7.1.3.3: Other significant adverse events. Additional special assessments discussed in Section 7.1.3.3 include CK elevations, drug-associated myopathies, amylase and lipase elevations, and lactic acidosis.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Measurement of vital signs was performed for subjects in all the pivotal studies at screening, baseline, and at Week 12, 24, and 52 for the first year. For subjects continuing into the second year of the trial, subsequent vital signs were taken at Week 76 and Week 104 or early termination visit. For post-treatment follow-up, vital signs were taken at each of the four monthly visits. These measurements included body weight, pulse, and blood pressure. Subjects in both treatment groups were well matched for baseline vital signs.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Blood pressure, pulse and body weight were evaluated for each the pivotal study, NV-02B-007 and the Phase 2b supporting studies, NV-02B-003/NV-02B-010, across treatment groups. No pooled analyses were performed.

7.1.8.3 Standard analyses and explorations of vital signs data

The assessment of vital signs identified no clinically relevant differences between the treatment groups. Results of the assessments raised no safety concerns.

7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable (see explanation under Section 7.1.8.3)

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable (see explanation under Section 7.1.8.3)

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Not applicable (see explanation under Section 7.1.8.3)

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were conducted by either the Applicant or the Medical Reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The potential of LdT to prolong QTc interval was assessed by *in vitro* evaluation for effects on the potassium channel encoded by the human ether-a-go-go-related gene (hERG). LdT had no effect on potassium channel current at concentrations up to 10,000 µM (2422 µg/mL) or 704 times the clinical Cmax exposure. Telbivudine elicited no adverse effects on blood pressure, heart rate, or ECGs at any dose up to 2000 mg/kg in cynomolgus monkeys.

The potential of LdT to prolong QTc interval was also assessed *in vivo* through study NV-0B-024, a Phase 1, randomized, partially-blinded, placebo and positive controlled, crossover study of the effect of LdT on cardiac repolarization (QT/QT_c interval duration) in healthy volunteers. This effect was evaluated at clinical (600 mg/day) and supra-therapeutic (1800 mg/day) LdT doses, using moxifloxacin, a drug known to prolong the QT interval, as a positive control.

There was no correlation between LdT plasma concentrations and an increase in QTcf interval for any analysis examined. The 15 time-matched placebo-adjusted changes from Baseline at Day 7 demonstrated that neither subjects receiving LdT 600 mg nor those receiving LdT 1800 mg

exceeded the threshold of 10 msec for the upper limit of the 95% confidence interval at any time point and that the changes were relatively consistent across the LdT treatment groups. Thus, there was no pattern of increasing placebo-adjusted change in QTcf from Baseline with dose or with time point. There was no apparent effect of any treatment on QRS or PR intervals. Maximum mean post-treatment QTcf was comparable in the placebo and LdT groups at 402-403 msec, but was higher in the moxifloxacin group at about 409 msec, from Baseline values of about 398 msec in all four groups.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable. Based on the results of NV-02B-024, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable. Based on the results of NV-02B-024, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.3.1 Analyses focused on measures of central tendency

Not applicable. Based on the results of NV-02B-024, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable. Based on the results of NV-02B-024, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Not applicable. Based on the results of NV-02B-024, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.9.4 Additional analyses and explorations

Not applicable. Based on the results of NV-02B-024, routine ECG monitoring was not conducted during the Phase 3 studies.

7.1.10 Immunogenicity

As a therapeutic nucleoside analogue, LdT is not expected to illicit an immune response. The applicant provided information from a murine local lymph node (LLNA tier 1) assay, in which topical application of telbivudine in DMSO providing up to approximately 750 mg/kg to the ears of BALB/c female mice failed to elicit changes in body weight gain, ear weight, lymph node weight or cell count or changes in immunological surface markers (CD4/CD8 for T cells, I-A/B220 for B cells, CD4/CD25 of IL-2 receptors on CD4 + T cells, CD4/CD69 for activated T cells and I-A/CD69 for activated B cells), indicating that telbivudine was not immunogenic. In addition, immunotoxicity studies have not been performed, but are planned. There was no clear evidence to suggest immunotoxicity in the repeated dose toxicity studies.

7.1.11 Human Carcinogenicity

Carcinogenicity studies were performed in rats and transgenic mice by oral gavage. Telbivudine's preclinical profile indicates that this drug does not pose a risk of carcinogenicity. Human carcinogenicity studies have not been conducted.

7.1.12 Special Safety Studies

The Applicant conducted a formal QT study to evaluate LdT's potential to prolong the QT interval. The results of this study are described above in section 7.1.9.1, Overview of ECG testing in the development program, including brief review of preclinical results.

Study NV-02B-011 is an ongoing, still-blinded, antiviral efficacy, safety, and tolerability study in adults with decompensated chronic hepatitis B. A total of 105 of 240 planned subjects have been enrolled in the study and have been on study as of the data cutoff for the 120-Day Safety Update (January 31, 2006). There have been eight deaths in this study, as of the data cut-off (January 31, 2006) and a total of 50 SAEs experienced by 35 subjects. Infections and infestations was the most reported SOC (16 subjects, 15.2%), including reports of bacterial peritonitis (6 subjects, 5.7%), cellulitis (3 subjects, 2.9%), sepsis (2 subjects, 1.9%), bacterial arthritis, gastroenteritis, chronic otitis media, pneumonia, septic shock, subdiaphragmatic abscess, and urinary tract infection (1 subject each, 1.0%). The second most commonly reported SOC was gastrointestinal disorders (9 subjects, 8.6%), including reports of ascites (3 subjects, 2.9%), gastrointestinal hemorrhage (2 subjects, 1.9%), duodenal ulcer, gastric varices hemorrhage, esophageal varices hemorrhage, and acute pancreatitis (1 subject each, 1.0%).

MO Comments
The eight deaths in NV-02B-011 are not unexpected in a population with decompensated liver disease and generally occurred just before or soon after randomization. The relatively larger number of SAEs in NV-02B-011 is not unexpected in this subject population with advanced cirrhosis and liver failure.

There were no other special safety studies submitted with this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Based on clinical experience with other therapeutic nucleoside analogues and the mechanism of action of LdT, it is not expected that LdT will be associated with any abuse potential or withdrawal phenomena. The occurrence of ALT flares after discontinuation of LdT (or other anti-HBV drugs) represents recurrence of uncontrolled HBV viremia and not a true withdrawal syndrome.

7.1.14 Human Reproduction and Pregnancy Data

LdT can cross both the blood-testes and placenta barrier. In the rabbit development toxicity studies, maternal toxicity (lower body weight and mean food consumption) was noted, in contrast with the control rabbits. One doe aborted and two does delivered their fetuses prematurely in the high dose group (1000 mg/kg/day). The study director attributed these pregnancy losses to maternal toxicity, not abnormal fetal development. In addition, one death was observed at 1000 mg/kg/day dose in pregnant rabbits. These animals had evidence of gastrointestinal irritation including reduced food consumption and body weight gain, abnormal feces, erosion on the stomach mucosal surface, red appearance and red fluid in the intestine, and distended stomach and intestine (with gas). The deaths were associated with high systemic exposure to LdT and the AUC value in the pregnant rabbits at 1000 mg/kg/day was 37 times higher than that in humans.

There is no controlled study data in pregnant women receiving LdT. Women enrolled in the clinical trials who became pregnant while on study drug were required to discontinue drug.

There have been 20 pregnancies reported in female subjects in the LdT clinical trials: 7 on LdT, 9 on lamivudine, 2 on telbivudine plus lamivudine combination treatment, and 2 in ongoing trials that have not yet been unblinded.

Twenty-four pregnancies have been reported in female partners of male subjects enrolled in the LdT clinical trials: 12 on LdT and 9 on LAM, 1 on LdT plus LAM combination treatment, 1 on LdT plus ADV treatment, and 1 in an ongoing trial that has not yet been unblinded.

Information regarding the outcome of pregnancies and treatment received is available for 31 of the 44 pregnancies. Table 7.1.14 A provides a summary of the outcomes of these pregnancies.

Table 7.1.14 A: Summary of Pregnancy Outcomes in LdT clinical trials

	Abortion			
	Spontaneous	**Induced**	**Healthy Live Birth**	**Unknown Outcome**
Subject pregnant				
LAM	3	3	1	2
LdT	2	4	0	1
LdT +LAM	0	1	0	1

LdT + ADV	0	0	0	0
Blinded Therapy	0	1	0	1
Subject's Partner Pregnant				
LAM	1	1	5	2
LdT	1	3	4	4
LdT + LAM	0	0	1	0
LdT + ADV	0	0	0	1
Blinded Therapy	0	0	0	1

Source: Table 7-4 in the 120-Day Safety Update Clinical Summary Document. Subjects were in the following trials: NV-02B-003, NV-02B-007, NV-02B-015, NV-02B-018, and NV-02B-024.

Studies in rats demonstrated that LdT was present in breast milk (milk/plasma AUC ratio of total radioactivity of 2.8.). Exposure to this drug *in utero* or in milk did not affect pup delivery or neonatal development in rats. The maximum amount of telbivudine that an infant could be exposed to by ingesting one liter of breast milk per day would be approximately 3.22 mg, (i.e. approximately 0.54% of a 600 mg adult dose, based on the average maximum (or mean Cmax) concentrations in humans after multiple daily 600 mg doses of telbivudine.). Experience with lactation in human subjects has not yet been obtained.

MO Comments
The Applicant has been encouraged to consider arrangements to participate in a national prospective registry for pregnant women who receive treatment for HIV (the Antiretroviral Pregnancy Registry). This seems appropriate since many of the antiretroviral drugs are nucleoside analogues and all other nucleoside analogues apsproved for treatment of HBV are included in the registry. The maternal toxicities seen in pregnant rabbits are not expected in humans, given the significantly lower levels of LdT exposure expected in pregnant women; however, monitoring adverse events during pregnancy will provide an opportunity to better assess maternal safety with LdT use.

7.1.15 Assessment of Effect on Growth

To date, all of the clinical trials of LdT have been conducted in adults. Therefore, no formal assessment of the effect of LdT on growth has been performed. Evaluation of LdT in children has not been initiated at this time.

7.1.16 Overdose Experience

There is no information on intentional overdoses, but two unintentional overdoses have been noted.

One subject in Study NV-02B-022 (the omnibus study) was reported to have taken three 600 mg LdT tablets/day for one month and then no study drug for one month due to a pharmacy labeling error. The subject was asymptomatic and experienced no event that qualified as an SAE during the time of overdose.

Another subject in Study NV-02C-004 was reported to have taken 4 days of study treatment incorrectly; the subject mistakenly took the pills in the columns of the blister pack instead of rows, causing him to take 7 pills of LdT, LdC, or placebo. As this study is ongoing, the data are blinded, and this subject's treatment assignment remains unknown. Laboratory results appeared normal after the unintentional mis-dose, and the subject was asymptomatic.

Study NV-02B-024 included a supra-therapeutic dose group that received 1800 mg of LdT for 4 days. The adverse event profile for this was supra-therapeutic dose group comparable to the adverse event profile seen for placebo in that study.

7.1.17 Postmarketing Experience

At this time, LdT has not been approved for use by any national regulatory authority so there is no post-marketing experience with the drug.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Total exposure to LdT is based on the sum of exposure from all studies (Phase 1-3 clinical trials). At the time of the NDA data cutoff date, April 19, 2005, a total of 1491 subjects had been exposed to any dose of telbivudine over the course of the clinical development program. At the time of the 120-day safety data cut-off date, November 1, 2005, however, 1523 subjects/subjects had been exposed to telbivudine 600 mg.

In the major safety population, at the recommended therapeutic dose of 600 mg/day, approximately 760 subjects have been treated with telbivudine for any duration. At the time of the NDA data cutoff date, the median exposure for LdT subjects in the pivotal trial, NV-02B-007 (n=680), was 60.2 weeks (range 2-106 weeks).

7.2.1.1 Study type and design/patient enumeration

Please refer to Table 4.2.A for a description of LdT clinical trials submitted for this safety review. Please refer to Section 7.1 for how these 24 clinical trials were ranked and divided for review. Briefly, pivotal Phase 3 study (NV-02B-007) was the primary source of safety data for this review.

7.2.1.2 Demographics

The following table, 7.2.1.2, provides demographic data for subjects, all of whom had chronic hepatitis B with compensated liver disease, included in the applicant's primary safety database, Study NV-02B-007.

Table 7.2.1.2: NV-02B-007: Demographic Characteristics of Subjects in Key Safety Cohort

Demographic Characteristic, n (%)	**Telbivudine** (n=680)	**Lamivudine** (n=687)	**Total Subjects** (n=1367)
Age (years)			
Median	34	35	34
Min, Max	16, 68	16, 68	16, 68
Gender, n (%)			
Male	507 (74.6)	529 (77)	1036 (75.8)
Female	173 (25.4)	158 (23)	331 (24.2)
Race, n (%)			
Asian	525 (77.2)	515 (75)	1040 (76.1)
Caucasian	98 (14.4)	111 (16.2)	209 (15.3)
African/African-American	7 (1)	10 (1.5)	17 (1.2)
Middle Eastern/Indian Subcontinent	14 (2.1)	11 (1.6)	25 (1.8)
Hispanic/Latino	4(0.6)	8(1.2)	12(0.9)
Other Races	32 (4.7)	32 (4.7)	64 (4.7)
Ethnicity n (%) [1]			
Other Asian or Pacific Islander	11(0.02)	15 (0.02)	26(0.02)
Chinese	381(56.0)	367(53.4)	748(54.7)
Filipino	4(0.6)	9(1.3)	13(1.0)
Japanese	0	1(0.2)	1(0.07)
Korean	54(7.9)	47(6.8)	101(7.4)
Malay	2(0.3)	4(0.6)	6(0.4)
Thai	50(7.4)	51(7.4)	101(7.4)
Vietnamese-Laotian	27(4.0)	28(4.1)	55(4.0)
Hawaiian-Pacific Islander	14(2.1)	7(1.0)	21(1.5)

Maori/Aboriginal	16(2.4)	19(2.8)	35(2.6)
Geographic Region			
Asia	445(65.4)	408(59.4)	853(62.4)
North America	74(10.9)	90(13.1)	164(12.0)
Europe	97(14.3)	108(15.7)	205(15.0)
Oceania	64(9.4)	81(11.8)	145(10.6)

Source: Medical Officer Review of electronic datasets, DEMOG & Table 10-1 in NV-02B-007 Study Report.
[1] Some subjects with Asian ethnicity were not categorized as Asian by race, including some who were listed as African-American or Caucasian.

The demographic features of the populations in the Phase 2b studies, NV-02B-003 and its follow-on study, NV-02B-010 are similar to the population in NV-02B-007. The Baseline demographic features in the multiple dose safety and tolerability clinical pharmacology (CP) studies are not compared to the target population because of the use of volunteers rather than hepatitis B subjects. Volunteers in these studies were predominantly young Caucasian males. Please refer to Section 6.1.4 for further discussion of the demographic representation in the pivotal trial.

7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3A summarizes the duration of exposure to study drug as of the most recent safety update to the NDA for subjects across the major safety study, NV-02B-007, supporting and other studies. This study continues to follow subjects still on blinded therapy or in four-month, off-treatment follow-up.

Table 7.2.1.3 A: Number of Subjects Exposed to LdT 600mg up to the 120-day safety data cut-off date (November 1, 2005)

Study	N	≥ 24 wks N(%)	≥ 52 wks N(%)	≥ 76 wks N(%)	≥ 104 wks N(%)	≥ 156 wks N(%)
003/010[1]	42	42 (100.0)	41(97.6)	35(83.3)	29 (6.0)	26(61.9)
003/010[2]	43	32(74.4)	29(67.4)	26(60.5)	20(46.5)	0
007	680	672(98.8)	663(97.5)	625(91.9)	169(24.9)	0
007/015	847	838(98.9)	828 (97.8)	625(73.8)	169(20.0)	0
015	167	166(99.4)	165(98.8)	0	0	0
011[3]	52	35(67.3)	17(32.7)	0	0	0
018	81	63(77.8)	0	0	0	0
019[3]	123	55(44.7)	0	0	0	0
022[4]	217	154(71.0)	132(60.8)	132(60.8)	128(59.0)	0
021[5]	24	0	0	0	0	0
02C-004	65	0	0	0	0	0

Source: Table 2-4 in 120-Day Safety Update Clinical Summary Document
[1] Subjects on LdT 600 mg or LdT 600 mg + 100 LAM in both NV-02B-003 & NV-02B-010.
[2] Subjects on LdT 400 mg or LdT 400 mg + LAM in NV-02B-003 who switched to LdT 600 mg or LdT 600 mg + LAM in NV-02B-010.
[3]Ongoing study is double blind. Exposure estimated as 50% of the total group.
[4]Exposure to LdT 600 mg includes treatment in NV-02B-007 or NV-02B-003/NV-02B-010 for those subjects who have received LdT while on NV-02B-022. Subjects who received LdT in previous studies but have not received LdT while on Study NV-02B-022 are not included.
[5]Study NV- 02B-021 was a clinical pharmacology study in which subjects received a single dose of study drug on two specific days

A summary of the duration of exposure for LdT 600 mg and LAM 100 mg monotherapies and LdT 600 mg plus LAM100 mg combination therapy up to the 120-day safety update cut-off date for the major safety population is provided in Table 7.2.1.3 B. The summary of exposure duration for the pooled data represents the first year of treatment. There was no difference in exposure duration between treatment groups in NV-02B-007 or in the pooled data during the first year of treatment. A significant difference in duration of exposure between treatment groups (p=0.003) in Study NV-02B-010 was not unexpected due to the disproportionate proportion of LAM-treated subjects that discontinued in the time period between the completion of NV-02B-003 and enrollment into NV-02B-010 compared to subjects who received telbivudine.

Table 7.2.1.3 B: Duration of exposure in weeks by treatment up to the 120-Day Safety Update Data Cut-Off Data in the Major Safety Studies Only

	Telbivudine 600mg	**Lamivudine 100mg**	**Combination**
NV-02B-007	(N=680)	(N=687)	-
Mean (SE)	88.8 (0.61)	88.0 (0.64)	-
Median	85.1	85.0	-
Min, max	1, 114	2, 115	-
Pooled NV-02B-007/NV-02B-015[1]	(N=847)	(N=852)	-
Mean (SE)	51.7 (0.16)	51.6(0.18)	-
Median	52.1	52.1	-
Min, max	1, 69	2, 63	-
NV-02B-010[2]	(N=19)	(N=44)[3]	(N=41)[4]
Mean (SE)	102.3 (12.04)	136.4(6.66)	145.1(6.47)
Median	99.1	160.2	163.6
Min, Max	9, 178	52, 182	41, 184

Combination = 100 mg/day LAM + 600 mg/day LdT; SE = standard error

[1] Duration of exposure up to Week 52.

[2] Subjects in NV-02B-010 had at least 52 weeks of therapy in NV-02B-003. Duration of treatment is cumulative from the Baseline of NV-02B-003 to last visit date for ongoing subjects, last dose date for subjects who completed or prematurely discontinued the study, or the day before treatment discontinuation for subjects who discontinued treatment for efficacy.

[3] Subjects who previously received LdT 400 mg are included.

[4] Subjects who previously received LdT 400 mg + LAM 100 mg are included

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The data from the pivotal Phase 3 controlled study, NV-02B-007, are used to provide the largest proportion of subjects for the safety claim and is considered the key study. Supportive data were provided from one controlled, Phase 2b study, NV-02B-003, and its longer term extension study, NV-02B-010, which enrolled subjects after receiving 52 weeks of treatment on the NV-02B-003 study.

Other studies reviewed for safety and described below were not integrated with the primary source data for one or more of the following reasons: short duration, inappropriate subject population (e.g. healthy volunteers), uncontrolled study, lack of CRFs, and/or inappropriate LdT dose (e.g. studied at doses below or above the to-be-marketed dose).

Additional supportive safety studies include a Phase 1/2a randomized, blinded, ascending dose trial for dose-finding, NV-02B-001, which provided safety, pharmacokinetic, and preliminary antiviral activity data in chronic hepatitis B subjects. This 28-day study provides safety data across a wide dose range of LdT from 25 mg to 800 mg once daily. Other supportive safety studies include NV-02B-005 and NV-02B-006, which have short durations of treatment but are included since these are in subjects with impaired hepatic and renal function. The QT/QTc prolongation study, NV-02B-24, addresses important cardiac safety parameters and is included though it is of short duration and in healthy volunteers.

Multiple dose drug interaction studies were performed for LdT in combination with LAM (NV-02B-002), valtorcitabine (Idenix's second investigational anti-HBV drug- NV-02C-003), pegylated interferon alfa-2 (NV-02B-012), adefovir (NV-02B-013) and cyclosporine (NV- 02B-023).

Additionally, several ongoing, still-blinded trials (NV-02B-011, NV-02B-015, NV-02B-018, and NV-02B-019) also provided limited data for the safety review, although there are limitations to interpreting the blinded data.

An integrated analysis would include subjects with chronic hepatitis B treated for >1 year with telbivudine monotherapy at 600 mg/day. As described below in Section 7.4.1.1, Pooled Data vs Individual Study Data, only two studies met these criteria: NV-02B-003 and NV-02B-007. The rationale for analyzing the safety data for these two studies is provided below in Section 7.4.1.1. All other studies described above were not integrated with the primary source data for one or more of the following reasons: short duration, inappropriate subject population (e.g. healthy volunteers), uncontrolled study, lack of CRFs, and/or inappropriate LdT dose (e.g. studied at doses below or above the to-be-marketed dose).

7.2.2.2 Postmarketing experience

As noted above, there is no post-marketing experience with LdT since it has not been approved for use in any country except Switzerland. There has not been enough post-marketing experience with

LdT since the Swiss approval in September, 2006 to draw conclusions based on post-marketing experience.

7.2.2.3 Literature

The Applicant included an extensive review of the literature related to treatment of chronic HBV, the emergence of virologic resistance with existing HBV treatments, pre-clinical reports, and correlation of different endpoints. This information was informative, including information on chronic progressive nephropathy in Sprague-Dawley rats. Several articles, however, were not critical to the NDA review of efficacy or safety.

In addition, both scientific literature and the labels of select lipid-lowering agents were reviewed for information on toxic myopathies and CK elevations.

7.2.3 Adequacy of Overall Clinical Experience

It is the opinion of this Medical Officer that the overall clinical experience with LdT presented in this NDA is adequate to assess the safety of the drug. Longer follow-up will be needed as clinical guidelines for duration of treatment may exceed the duration of initial drug testing. Subjects enrolled in the studies reported in the NDA continue to be followed either in the pivotal studies or in rollover or long-term observational studies conducted by the Applicant.

In general, an adequate number of subjects were enrolled in the pivotal study and exposed to study drug to assess the safety of LdT compared to LAM. As noted previously, there were not adequate numbers of blacks/African Americans, Hispanics and subject from other non-Asian/non-White backgrounds, enrolled in the clinical trials to be assured that the safety profile in these subgroups is similar to those of other racial groups. The doses and duration of exposure in nucleoside-naïve subjects were reasonable and adequate to support initial review of safety. The safety of longer-term dosing will be evaluated in future submissions as subjects continue dosing through the second year of the Phase 3 and other supporting studies and rollover into other protocols. The design of the pivotal studies utilizing LAM as an active control was appropriate to answer the most important questions regarding comparative safety and efficacy.

The potential toxicities identified in pre-clinical testing such as gastrointestinal intolerance and peripheral and sciatic nerve findings and were evaluated throughout the Phase 2 and 3 drug development programs. There was a very slight difference (~ 1.5%) in related clinical toxicities (e.g. diarrhea/loose stools, sensory symptoms) between the treatment arms, with the slightly higher frequency occurring among LdT subjects. Evaluation for these and other clinical safety signals, including myopathy and CK elevations, is ongoing. The four cases of myopathy among subjects in the LdT drug development program highlights the need for additional attention to identifying the possible predisposing factors for the development of this particular adverse event. The potential class effect of nucleoside analogues, lactic acidosis, was not evaluated prospectively but was evaluated using a search of the pivotal trial safety database as described above in Section 7.1.3.3, Other Significant Adverse Events.

Similarly, the anticipated occurrence of ALT flares, a complication of any active treatment of chronic HBV was evaluated throughout the pivotal studies. The pivotal studies were limited to subjects with compensated liver disease. It is possible that subjects with decompensated liver function may have a different safety profile and an ongoing study, NV-02B-011, is evaluating this issue.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special animal and *in vitro* testing was adequate. Please refer to Section 3.2 and Dr. Ita Yuen's review for details of preclinical program.

7.2.5 Adequacy of Routine Clinical Testing

It is the opinion of the Medical Officer that the routine clinical and laboratory testing conducted during the pivotal and supportive studies was generally adequate to assess safety. There were notable gaps in laboratory testing, however. Nucleoside analogues, as a class, have been associated with lactic acidosis. Laboratory tests needed to detect lactic acidosis (e.g. bicarbonate, potassium, sodium, chloride) were not routinely collected during the Phase 2b and Phase 3 clinical trials. In addition, there was a high rate of CK elevations in the Phase 3 registration trial, raising the need for adequate laboratory testing to detect or rule out rhabdomyolysis (e.g. urine myoglobin, BUN, electrolytes, glucose). These laboratory tests were not routinely during the Phase 3 clinical trials. Otherwise, the timing of clinical and laboratory tests were appropriate for the study populations and the disease being studied.

MO Comment
Given the relatively limited (in terms of time) data we have on the possibility of the possible complications of LdT-associated CK elevations, including rhabdomyolysis, Idenix will be encouraged to expand monitoring for rhabdomyolysis among subjects with Grade 3 or 4 CK elevations.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pre-clinical and clinical evaluations of metabolic, clearance, and potential drug interactions were adequate for the class of drug and indication being studied. For a more detailed evaluation of these issues, refer to the Clinical Pharmacology/Biopharmaceutics Review by Dr. Jennifer Zheng and the summary of these findings included in Section 5 Clinical Pharmacology.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

In general, the Applicant's efforts to evaluate potential AEs that might arise with any new drug were adequate. The evaluation of potential hepatotoxicity was an integral part of the LdT drug

development program since in the chronic HBV study populations changes in liver enzymes were used to evaluate both efficacy and safety.

Preclinical investigations have not demonstrated a finding associated with mitochondrial toxicity and therefore, LdT was believed to be unlikely to produce significant toxicity related to this mechanism. Nevertheless, the applicant's efforts to evaluate AEs that might be expected with the use of nucleoside analogues (lactic acidosis) was inadequate, as discussed above in section 7.1.3.3, Other Significant Adverse Events and section 7.2.3 Adequacy of Overall Clinical Experience. There were at least four cases of myopathy among LdT subjects in the LdT drug development program, raising the possibility of a mitochondrial toxicity. The applicant's investigation and follow-up of these subjects was appropriate, but, in the case of one subject (NV-02B-007: Subject #071-043), inadequate, due to difficulty obtaining follow-up information from the investigator.

The Applicant's efforts to evaluate other AEs that might be expected with the use of drug used in the treatment of chronic HBV (ALT flares) were adequate.

The Applicant's evaluation of ALT flares was consistent with the approach suggested by the Review Team during the drug development program. This analysis concluded that LdT treated subjects experienced a similar frequency of ALT flares as LAM-treated subjects for the first 24 weeks of treatment. After 24 weeks of treatment, LdT-subjects experienced fewer ALT flares than LAM-treated subjects. Evaluations of these toxicities with longer-term dosing are on-going. Few subjects have discontinued study drug, limiting the ability to evaluate the occurrence of off-treatment ALT flares.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of the data available for conducting the safety review was adequate. In the adverse event listings datasets, there were 12.6% (173/1367) of study subjects with missing data for the date of onset (ONSETDT). In the majority of these cases, the month (ONSETMN) and year (ONSETYR) of onset and/or resolution, but the day (ONSETDY) was missing. Similarly, 10.9% (149/1367) of study subjects with available data for the month (RESOLVMN) and year (RESOLVYR) of clinical adverse event resolution had missing data for the day (RESOLVDY) of adverse event resolution. The review approach to this missing data is described above in Section 7.1, Methods and Findings. In summary, when ONSETDY was missing, but ONSETMN and ONSETYR were available, ONSETDY was assumed to be the first day of the month. Similarly, when RESOLVDY was missing, but RESOLVMN and RESOLVYR were available, RESOLVDY was assumed to be was assumed to be the 30th day of the month (or the 28th day for February).

Otherwise, the proportions of study subjects who had other types of missing data were relatively small and considered acceptable. Follow-up of subjects enrolled in the pivotal studies was also acceptable with very few subjects discontinuing study for unknown reasons.

7.2.9 Additional Submissions, Including Safety Update

The Applicant submitted a Safety Update Report on May 1, 2006 that reported additional safety findings since the data inclusion cut-off dates set for NDA 22-011. A data cut-off date of November 1, 2005 is set for data collected in the key safety studies and ongoing studies[65], whereas a data cut-off date of January 31, 2006 is used for reports of new serious adverse events and updates to previously reported SAEs and deaths. In addition, data were provided for two studies, NV-02B-021 and NV-02C-004[66], which were initiated between the data cut-off date of the original application and cut-off date of this safety update.

Data from the NV-02B-015 study are newly available for the 120-day safety update. This ongoing phase 3 study is being conducted in China for the purpose of Chinese registration. Complete data up to Week 52 of the study were available by the 120-day safety update cut-off date, and these data were pooled with Baseline to Week 52 data from Study NV-02B-007.

The new data in this submission was incorporated into several sections of the primary safety review as described above in the following sections:

- 7.1.1: Deaths
- 7.1.2: Other Serious Adverse Events
- 7.1.3.1: Overall profile of dropouts
- 7.1.3.2: Adverse Events associated with dropouts
- 7.1.3.3: Other Significant Adverse Events
- 7.1.4: Other Search Strategies
- 7.2.1.3: Extent of Exposure
- 7.1.5.4: Common Adverse Event Tables
- 7.1.5.6 Additional Analyses and Explorations
- 7.1.7.3.2: Analyses focused on outliers or shifts from normal to abnormal
- 7.1.7.4: Additional Analyses and Explorations
- 7.1.12: Special Safety Studies
- 7.1.14: Human Reproduction and Pregnancy
- 7.1.16: Overdose Experience

Review of the 120-Day Safety Update focused primarily on SAE, death, AE, related discontinuation, and Grade 3-4 laboratory abnormality-related safety updates associated with the pivotal trial, NV-02B-007, the Chinese registrational trial, NV-02B-015 (first 52 weeks), the supporting extension study, NV-02B-010 and some of the ongoing studies, particularly NV-02B-011 (subjects with decompensated liver disease).

In addition to the data provided in the 120-Day Safety Update, the Applicant provided several responses to FDA requests for information throughout the review, including several requests for revised structuring of datasets which were submitted through email communications which were later added as electronic submissions to the NDA.

The information provided through these responses to FDA requests for information is interspersed

[65] Key safety and ongoing studies include: NV-02B-003, NV-02B-007, NV-02B-010 (extension study-HBeAg-positive only), NV-02B-011 (subjects with decompensated disease-ongoing), NV-02B-018(open-label, HBeAg-positive only-ongoing), NV-02B-019(double-blind-ongoing), NV-02B-022 (open-label-rollover study), and NV-02B-015 (Chinese registrational trial).

[66] NV-02B-021 is a Phase 1 bioequivalence of two oral formulations in healthy male Chinese adults; NV-02C-004 is a study comparing LdT monotherapy to combination therapy of LdT plus valtorcitabline (LdC) in adults with HBeAg-positive compensated chronic hepatitis B (77 enrollees)

throughout the review, with particular emphasis on Section 7.1.3.3, Other Significant Adverse Events.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety profile of LdT was similar to that of LAM in pivotal trial, with the exception of CK elevations and myopathy among LdT subjects and late ALT flares among LAM subjects. The pattern of commonly reported AEs was relatively high with 75% of LdT subjects and 71% of LAM subjects reporting some AE.

If all AEs of any intensity are considered, the most commonly reported events in LdT-treated subjects included: upper respiratory infection, fatigue/malaise, nasopharyngitis, headache, CPK increased, abdominal pain, and cough (see Table 7.1.5.4A). Many of these events are common in the general population and in the population of patients with chronic HBV. Because the pivotal study used LAM as the active control, it is somewhat difficult to determine true rates of LdT-related AEs. Even though the AE profile for LdT is similar to that of LAM does not mean that the AEs occurring in both treatment groups are not drug-related.

Four categories of events deserve increased attention because of the potential seriousness of the events or signals from animal toxicology studies. To date, only CK elevations and myopathy with muscle weakness have been shown to occur more frequently among LdT-treated subjects.

7.3.1 Acute Exacerbations of Hepatitis (ALT Flares)

ALT flares have been described during treatment with all of the approved drugs for chronic HBV and after discontinuation of drugs that have activity against HBV. During the LdT development program, these events were tracked both during treatment and off-treatment follow-up.

ALT flares were documented infrequently in subjects during the on-treatment period but occurred more often in subjects receiving LAM; 3% of LdT-treated subjects and 5% of LAM -treated subjects experienced a flare, based on AASLD flare criteria. ALT flares more commonly resulted in study drug discontinuation among LAM subjects than LdT subjects. There was very little limited data to estimate the risk of hepatitis B exacerbation after treatment discontinuation; however, the available data do suggest that persons who discontinue therapy may be at increased risk for post-treatment flares, relative to persons who start another form of anti-HBV treatment.

The analysis of ALT flares is discussed in more detail in Section 7.1.3.3, Other significant adverse events.

7.3.2 Creatine Kinase Elevations and Drug-Associated Myopathy

Because LdT-associated CK elevations were identified in the Phase 2b study and the pivotal trial, CK-related AEs were reviewed in detail for this review. In NV-02B-007, CK elevations occurred in both treatment arms; however median CK levels were higher in LdT-treated subjects by Week 52. Grade 1-4 CK elevations occurred in 72% of LdT-treated subjects and 42% of LAM-treated subjects, whereas Grade 3/4 CK elevations occurred in 9% of LdT-treated subjects and 3% of LAM-treated subjects. While most CK elevations were asymptomatic the mean recovery time for

the CK elevations was longer for subjects on LdT than subjects on LAM. While there was not a uniform pattern with regard to the type of adverse event and timing with respect to the CK elevation, 8% of LdT-treated subjects with Grade 1-4 CK elevations experienced a CK-related adverse event[67] (within a 30-day window) compared to 6% of LAM-treated subjects. Furthermore, 9% (5/55) of the LdT-treated subjects with a CK-related adverse event interrupted or discontinued study drug to the adverse event; these subjects recovered after study drug discontinuation or interruption. Less than 1 % of LdT-subjects overall were diagnosed with myopathy, including muscle-weakness; those subjects who discontinued study drug recovered. There have not been any known clinical cases of rhabdomyolysis, with or without renal failure, in the LdT development program.

There seems to be an emerging pattern of a cumulative, toxicity resulting in myopathy, including muscle weakness, for subjects on LdT. The myopathy occurs with LdT use greater than 8-10 months. Looking beyond the subjects described above, there was, overall, a greater proportion of adverse events related to muscle weakness on the LdT arm (7 subjects, 0.8%) than on the LAM arm (2 subjects, 0.2%) in NV-02B-007. No subjects on LAM discontinued or interrupted study drug due to an adverse event related to muscle weakness in either the Chinese (NV-02B-015) or American (NV-02B-007) LdT registrational trials.

The possible mechanism of LdT muscle toxicity is also unclear. While preclinical testing for mitochondrial toxicity was negative, there are additional assessments that may provide additional clarification regarding possible mitochondrial toxicity. (Please refer to section 6.1.5, Clinical Microbiology, above or the Microbiology Review by Dr. Sung Rhee).

There is also insufficient data to determine whether or not the subjects who developed drug-associated myopathy share a common predisposing risk factor. Additional information on subjects with this clinical presentation will collected in the ongoing LdT trials, to allow better characterization of this phenomenon. The analysis of CK elevations and drug-associated myopathy is discussed in more detail in Section 7.1.3.3, Other significant adverse events.

7.3.3 Neuropathy

Because spinal cord and sciatic axonopathy was noted in all LdT dose groups (including controls) in monkeys, neurologic AEs were reviewed in detail for this review (refer to Section 7.1.4, Other search strategies). Sensory-related AEs were evaluated in the pivotal study and rates were similar across treatment groups. The proportion of subjects reporting any sensory symptom[68] was 3% for LdT-treated subjects and 2% for LAM-treated subjects; this difference is largely explained by the higher rate of dysgeusia among LdT-treated subjects. In short, there were no significant differences between the treatment arms. No significant pattern of LdT-related sensory AEs could be identified. These events will continue to be evaluated in the ongoing Phase 3 studies and other clinical trials assessing long-term dosing of LdT.

7.3.4 Nephropathy

The highest LdT dose group (2000 mg/kg/day), among Sprague-Dawley rats had a higher rate of mortality due to chronic progressive nephropathy (CPN), raising questions regarding the role of

[67] Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, and pain in extremity.
[68] Includes preferred terms: dysesthesia, dysgeusia, sensory loss, intercostal neuralgia, neuropathic pain, polyneuropathy, sciatica, sensation of heaviness, paraesthesia, hypoaesthesia, hypoaesthesia oral, paraesthesia oral, and neuralgia

LdT in the development of this renal toxicity. In clinical studies with LdT, there was no evidence for a pattern of LdT-associated nephropathy in the Phase 1 and 2 trials or the Phase 3 registrational trial. Only one case of nephrotic syndrome in an LdT-treated subject (IND 60459 Serial # 269) has been reported and that subject had multiple pre-existing risk factors (diabetes mellitus, hypertension, baseline proteinuria). Based on current evidence, it seems unlikely that LdT worsens renal function in subjects with chronic hepatitis B and normal renal function. It is possible, however, that as more subjects with chronic hepatitis B and compromised renal function or a high risk for compromised renal function (e.g diabetes, hypertension, elderly, etc.) initiate treatment with LdT, an adverse event profile of nephropathy may emerge.

7.3.5 Gastrointestinal

As noted above in Section 3.2, Animal Pharmacology/Toxicology, high LdT doses led to some gastrointestinal (GI) intolerance in pregnant rabbits, non-pregnant monkeys, and rats. One pregnant rabbit died at the 1000 mg/kg/day dose, while two had premature deliveries and one aborted. These animals showed evidence of gastrointestinal irritation, including reduced food consumption and less body weight gain, abnormal feces, erosion on the stomach mucosal surface, reddish fluid and appearance in the intestine, and distended stomach and intestine (with gas) leading the study investigator to attribute the negative pregnancy outcomes to maternal toxicity. The death occurred after more than 10 doses of LdT; hence GI irritation could be a dose limiting toxicity in rabbits. The AUC value in the pregnant rabbits at 1000 mg/kg/day was 2-3 times higher than those at the highest doses studied in mice, rats, and monkeys, and 37 times higher than that in humans. Unlike the pregnant rabbits and the rats, the mice did not demonstrate GI intolerance.

One subject in the pivotal trial discontinued LdT due to an AE in the Gastrointestinal Disorders SOC. This subject (Subect # 005-007) was a 43 year old Asian male who developed nausea and loose stools after 389 days on study drug. This AE was ongoing with the subject eventually discontinuing LdT on Study Day 446. His GI symptoms resolving approximately 43 days after study drug discontinuation.

In addition, while approximately 30% of subjects in the pivotal clinical trial (NV-02B-007) experienced at least one adverse event (AE) in the Gastrointestinal Disorders System Organ Class (SOC), the rate of occurrence of these AEs was equal between the treatment arms (30% LdT and 30% LAM). While, the preclinical GI toxicity may be concerning at high LdT exposures, the AUC associated with this GI toxicity is 37-times higher than that in humans. GI toxicity is unlikely to be dose limiting in humans. It is unknown, however, whether or not patients with pre-existing gastrointestinal disease or patients who experience a significant LdT overdose may be at risk for more severe GI toxicities.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The data from the pivotal Phase 3 controlled study, NV-02B-007, are used to provide the largest proportion of subjects for the safety claim and is considered the key study. The subjects enrolled were from the target population of primary interest and also provide the primary efficacy data. A sufficient number of subjects were enrolled in this study to allow subgroup analyses. The rate and type of adverse events in the key safety population and in the demographic subgroups, the change over time in the pattern of adverse events, and any drug-drug or drug-disease interactions are explored. Pooling of data with the other small group of subjects available, such as NV-02B-003, was not considered useful because the study would not contribute sufficient subjects to change the conclusions reached in NV-02B-007. For the original telbivudine NDA submission, an integrated analysis would include subjects with chronic hepatitis B treated for >1 year with telbivudine monotherapy at 600 mg/day. The telbivudine development program contains only two completed controlled studies with subjects meeting these criteria: the Phase 2b trial, NV-02B-003 which included only 22 chronic hepatitis B HBeAg-positive subjects randomized to telbivudine 600 mg/day monotherapy, and the large, global, Phase 3 trial, NV-02B-007.
The data from the two studies are presented separately because, as stated above, the data from the smaller Phase 2b study are unlikely to affect the conclusions of the large pivotal trial, and the value of the data from the smaller Phase 2b trial for obtaining an independent assessment of safety would be lost.

The Applicant presented data and datasets from NV-02B-003, NV-02B-010, and other remaining studies by study.

MO Comments
This Medical Reviewer agrees with the Applicant's rationale that pooling data from smaller studies, such as NV-02B-003 would not contribute sufficient subjects to change the safety conclusions reached in NV-02B-007.

Since the NDA data cut-off date, all subjects in Study NV-02B-015 have completed the Week 52 visit, and these data have been pooled with the first year data of the primary pivotal study, NV-02B-007, for the purpose of the 120-day safety update. These data are well suited to pooling as the study designs, dosing, and inclusion/exclusion criteria of both studies are identical, with the exception of a requirement for Week 52 liver biopsies in NV-02B-007. First year data for NV-02B-007 was provided in the original NDA submission, therefore, the pooled data provided in the 120-Day Safety Update contain some data previously presented.

7.4.1.2 Combining data

In pooling data for the 120-Day Safety Update, the applicant combined the numerator events or laboratory abnormalities and denominators for NV-02B-007 and NV-02B-015. No selective weighting of events or studies was performed.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The results of the NV-02B-001 Phase 1/2a trial indicated that LdT exhibits dose-related virologic effects in HBV-infected subjects receiving LdT once daily at escalating doses from 25 to 800 mg for 28 days. There was no appreciable dose-related pattern of clinical adverse events or laboratory abnormalities. LdT was generally well tolerated for four weeks across the range of doses evaluated. In NV-02B-003, the Phase 2b dose-finding study, the overall incidence of AEs, and the incidence of the various specific types of AEs, were similar across the five randomized treatment groups. There was no specific pattern of AEs with respect to the dose of LdT administered (LdT 400mg versus LdT 600mg). Does dependency for adverse findings could not be evaluated in the NV-02B-007 global registrational trial because all LdT subjects received a fixed dose of study drug, LdT 600mg once daily.

7.4.2.2 Explorations for time dependency for adverse findings

Other than the exploration related to the timing of ALT flares and CK elevations, no formal evaluation of time dependency for adverse findings was conducted. For a description of the evaluation of ALT flares and CK elevations, refer to Section 7.1.3.3, Other significant adverse events.

7.4.2.3 Explorations for drug-demographic interactions

Both the Applicant and this Medical Reviewer Applicant conducted various subgroup analyses of clinical adverse events and laboratory abnormalities across the treatment arms. Although there were some differences based on different demographic parameters (gender, age, race, etc) these were generally comparable across the 2 treatment groups and did not appear to be drug-specific.

7.4.2.4 Explorations for drug-disease interactions

There was no formal analysis conducted to explore drug-disease interactions for LdT used in different stages of HBV. All study subjects reported in the NDA safety data had compensated liver disease and a different safety profile or level of tolerance of LdT may be identified when Study NV-02B-011 in subjects with decompensated liver disease is completed.

7.4.2.5 Explorations for drug-drug interactions

Since LdT is primarily excreted unchanged in the urine, few drug-drug interactions were anticipated. Because of low potential for CYP450-mediated interactions for LdT, the drug-drug interaction studies have focused on drugs that are likely to be used concomitantly in some hepatitis B subjects receiving LdT, in particular other nucleoside/nucleotide antivirals (LAM, ADV),

peginterferon alfa-2a, investigational valtorcitabine, and cyclosporine A, an immunosuppressive used in HBV-infected subjects undergoing solid organ transplantation or with autoimmune disorders. Co-administration of LdT with LAM, adefovir dipivoxil, valtorcitabine, peginterferon alfa-2a or cyclosporine A is well tolerated and does not appear to significantly affect the pharmacokinetics of either drug. Subjects who required nephrotoxic or hepatotoxic drugs as part of their treatment were prohibited from enrolling in the pivotal studies. For more information regarding these drug-drug interactions, please refer to the Clinical Pharmacology/Biopharmaceutics review conducted by Dr. Jennifer Zheng.

7.4.3 Causality Determination

The safety profile of LdT was generally similar to that of LAM in the key clinical safety studies, with the exception of CK elevations (LdT), on-treatment ALT flares (LAM), and myopathy (LdT). AEs were commonly reported but there were few differences in the pattern of AEs reported by LdT-treated subjects compared to LAM-treated subjects. Many of these events are common in the general population and in the population of subjects with chronic HBV.

Among the clinical and laboratory events most commonly considered LdT-related were: fatigue/malaise, diarrhea/loose stools, pyrexia, Grade 1-4 CK elevations, Grade 1 creatinine elevations, and Grade 1-2 ALT/ AST elevations. As described in Section 7.1.3.3, Other Significant Adverse Events, additional search strategies also revealed a slightly higher occurrence of sensory (3.4% vs. 1.9%) and muscular weakness-associated (0.8% vs. 0.2%) symptoms among LdT subjects. It is possible that these events are causally related to LdT (and LAM); however, without a long-term comparison of LdT to placebo in subjects with chronic HBV it may be impossible to be certain of the exact contribution of LdT. At this time, a placebo-controlled long-term study of chronic HBV treatment would be considered unethical.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Applicant seeks approval for treatment of chronic HBV at doses of LdT 600mg once daily in nucleoside-naïve subjects. The submitted pivotal study and supporting Phase 2b study support these doses.

There were no differences in drug exposure based on gender. There are no significant race-related differences in LdT pharmacokinetics and no dose adjustment based on race is necessary.

The once daily dosing interval is well-supported by the PK data submitted. Additionally, food efect studies suggest that LdT absorption and exposure were unaffected when a single 600 mg dose was

administered with a high-fat (54.6 g), a high-calorie (950 kcal) meal. It will be recommended that LdT may be dosed on with or without food.

The dose- and systemic exposure-response relationships were characterized by a standard Emax model using viral load reduction at week 4 from baseline expressed as percent reduction and log10 reduction as pharmacodynamic variables. Both the dose- and exposure-based approaches indicate a near maximal virologic response with LdT doses in the range of 400-800 mg/day. Specifically, data from the Phase 2b trial, NV-02B-003, indicated that the 400 mg and 600 mg daily doses afforded similar antiviral efficacy. To maximize antiviral efficacy and reduce the emergence of viral resistance, a dose of 600 mg/d was chosen for the Phase III program. This dose (600 mg/d) was selected based on both the Emax model, which predicted approximately a 0.2 log10 (~40%) greater antiviral effect over the 400 mg/d dose, and the NV-02B-001 and NV-02B- 003 safety observations, which indicated a lack of dose-related safety concerns. Refer to Sections 5.3 Exposure-Response Relationships and 6.1.3 Study Design, for more complete discussion of dose selection. The Phase 3 clinical trial supports the non-inferiority of the efficacy, safety, and tolerability of LdT compared to LAM in nucleoside-naïve populations.

The Applicant evaluated LdT exposure in subjects (without chronic hepatitis B) with renal impairment including those requiring hemodialysis. Results from this study confirmed that the pharmacokinetics of LdT are renal function dependent; progressively higher plasma exposure accompanied with reduced urine excretion was observed as renal function deteriorated, in particular, in subjects with moderate to severe renal impairment including ESRD subjects requiring hemodialysis. The LdT renal clearance is directly proportional to creatinine clearance, and approaches total plasma clearance, indicating that renal clearance is the major elimination pathway for LdT. Additionally, a 3.5-4 hour hemodialysis session removes approximately 23 % of systemic exposure of LdT.

Study results indicate that subjects with mild renal impairment have comparable exposure compared to normal subjects; therefore, patients with mild renal impairment do not require dose adjustment. In contrast, dose interval adjustment is warranted in subjects with moderate to severe renal impairment to achieve comparable exposure to normal subjects as shown below in Table 8.1A.

Table 8.1.A: Proposed Dose Adjustments for LdT in Patients with Renal Impairment

Creatinine clearance (mL/min)	Dose of LdT
≥ 50	600 mg once daily
30 – 49	600 mg once every 48 hours
< 30 (not requiring dialysis)	600 mg once every 72 hours
ESRD	600 mg once every 96 hours

Dr. Jenny H. Zheng, Clinical Pharmacology/Biopharmaceutics reviewer, confirmed the Applicant's results and agreed with their dose interval adjustment for patients with renal impairment.

8.2 Drug-Drug Interactions

LdT is excreted mainly by passive diffusion so the potential for interactions between LdT and other drugs eliminated primarily by renal excretion is low. However, because LdT is eliminated

primarily by renal excretion, co-administration of LdT with drugs that alter renal function may alter plasma concentrations of LdT.

8.3 Special Populations

As noted above, the Applicant evaluated LdT exposure in subjects with renal impairment in study, NV-02B-006, including those requiring hemodialysis. Subjects requiring continuous ambulatory peritoneal dialysis (CAPD) were not evaluated. Specific dosage recommendations for patients with renal impairment are included in Section 8.1 Dosing Regimen and Administration.

Clinical studies of LdT did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently from younger subjects. In general, caution should be exercised when prescribing LdT to elderly subjects considering the greater frequency of decreased renal function due to concomitant disease or other drug therapy. Renal function should be monitored in elderly subjects and dosage adjustments should be made accordingly.

Study NV-02B-005 investigated the effect of hepatic impairment on LdT pharmacokinetics and no significant differences in drug exposure were identified in this subgroup. Dose adjustment is not necessary in subjects with hepatic impairment.

The safety and efficacy of LdT in liver transplant recipients are unknown. The steady-state pharmacokinetics of LdT were not altered following multiple dose administration in combination with cyclosporine.

LdT has not been investigated in co-infected hepatitis B subjects (e.g., subjects coinfected with HIV, HCV or HDV. LdT is not active against HIV-1 (EC_{50} value >100 μM) in *in vitro* studies and was not antagonistic to the anti-HIV activity of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine, but it is not known whether or not dosage adjustment is needed in subjects coinfected with HIV, HCV or HDV.

The clinical trials did not assess LdT in women who were pregnant or breastfeeding. In the rabbit developmental toxicity study, the highest LdT dose, 1000 mg/kg/day, caused maternal toxicity, as evidenced by lower mean food consumption and body weight compared to concurrent control rabbits. One doe aborted and two does delivered their fetuses prematurely in the high dose group. While these findings may have been due to a direct effect of LdT treatment, it was judged by the study director as secondary to maternal toxicity. There was no abnormal fetal development in either the rat or rabbit studies. In the post-marketing stage, it is very likely that LdT will be taken by women who may be or may become pregnant while receiving the drug.

To date, the use of LdT for the treatment of chronic HBV in pediatric subjects has not been evaluated. Please see Section 8.4, Pediatrics, below for further discussion of the Applicant's proposed pediatric development plan. A pediatric development program is essential to allow safe use of the drug in this population and limit the potential dangers of off-label use.

MO Comments
The Applicant has been encouraged to consider arrangements to participate in a national prospective registry for pregnant women who receive treatment for HIV (the Antiretroviral Pregnancy Registry). This seems appropriate since many of the antiretroviral drugs are nucleoside analogues and all other nucleoside analogues apsproved for treatment of HBV are

included in the registry.

8.4 Pediatrics

To date, the use of LdT for the treatment of chronic HBV in pediatric subjects has not been evaluated. Although HBV vaccination has been universally recommended for infants in the U.S. and many other countries, there remains a significant burden. The Applicant included a request for deferral of pediatric studies with their NDA application. In this request, the Applicant proposes to to be used in the Phase I PK dose finding trial and a pediatric Phase III safety and efficacy trial. This formulation will consist of the pre-validation and validation batches of the final market image.

The Applicant proposes the following pediatric development plan for LdT:

- Open-label, single dose Phase I study (in a high HBV prevalence region) to evaluate the pharmacokinetics and safety of LdT in pediatric and adolescent subjects (ages 2-17 years of age) with chronic hepatitis B infection.
    - Eligible subjects would be stratified into three age groups (stratum 1: 2 – 6 years; stratum 2: 7-12 years; and stratum 3: 13 – 17 years) with 8 subjects in each age stratum.
    - Two doses (15 and 25 mg/kg) of LdT would be evaluated in each age stratum except for adolescents for whom the full dose (600 mg total dose) will be administered.
    - Proposed sampling of approximately 120 hours, a choice is dictated by the LdT PK characteristics (T1/2=40 hr).

- Phase III Safety and Efficacy Pediatric Study
    - Juvenile animal toxicity studies of LdT will be conducted to support this Phase III trial.
    - Eligible subjects: otherwise healthy children and adolescents between 2 and 17 years of age, who show evidence of chronic HBV infection
        - (HBsAg positive on at least two occasions six months apart) and who are HBeAg positive, who have persistently abnormal ALT levels of > 1.3 x ULN but less than 500 IU/L, and who have HBV DNA levels of greater than 106 copies/mL.
        - Subjects randomized to LdT or placebo in a 2:1 ratio and treated for 52 weeks.
        - The primary endpoint: virologic response (HBV DNA <105 copies/mL and HBeAg loss).
        - Safety evaluations would include the monitoring of AEs and laboratory evaluations (biochemical and hematological) at every study visit.
            - Secondary endpoints: ALT normalization, HBeAg seroconversion, and viral breakthrough and resistance.

The Applicant has also requested a partial waiver for conducting pediatric studies in the neonatal age group (ages 0 through 2 years). The majority of children with chronic HBV infection within this age group will have been infected perinatally and, although their HBV DNA levels are high, they tend to have normal transaminase levels with minimal liver disease, a profile associated with sub-optimal responses to therapy.

Prior to NDA submission, the Applicant submitted an outline of their pediatric drug development plan and a synopsis for a proposed pediatric PK study under IND 60459, S203. In response, the Division of Antiviral Products submitted a letter to the Applicant requesting additional details regarding their pediatric drug development plan, including proposed protocols for safety and efficacy studies and full study protocols for the pediatric PK study summarized in their submission. Additionally, the Applicant was informed that our clinical pharmacology team had determined that at least twelve pediatric subjects are necessary per age stratum for a pediatric PK study and that the sample size should be increased as necessary for appropriate characterization of PK across the intended age range.

During a LdT labeling teleconference on October 12, 2006, the Applicant was notified that this NDA, as an application for a new molecular entity, is required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. The Applicant understands that the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) will be outlined in a Written Request for pediatric exclusivity subsequent to the action date for this NDA submission and are considered required postmarketing study commitments.

MO Comments
We believe the Applicant should proceed with a pediatric development plan and are pleased that a [redacted] *It is imperative to obtain PK, safety, and efficacy data in pediatric subjects as quickly as possible* [redacted] *The request for deferral of pediatric studies submitted with the NDA, however, did not incorporate the information requested in the letter sent by this Division requesting additional details on their pediatric drug development plan.*

The primary endpoint proposed for the Phase 3 pediatric safety and efficacy study is unacceptable. This will be addressed in a response to full study protocols that will be submitted for any Phase 3 Pediatric Safety and Efficacy study.

Although we have not yet received a more detailed proposal for pediatric drug development from the Applicant, a formal Written Request for pediatric studies will be issued to the Applicant. Please see Section 9.3.2, Post-Marketing Commitments, for a description of the pediatric studies that are being deferred under the Pediatric Research and Equity Act (PREA).

8.5 Advisory Committee Meeting

An Advisory Committee Meeting was not held to review the use of LdT for the treatment of chronic Hepatitis B in adults.

8.6 Literature Review

Literature reviewed for this NDA included current literature on the incidence and management of drug-associated myopathy and drug-associated creatine kinase elevations. In addition, the Applicant provided a literature review related to Hepatitis B infection with the NDA.

8.7 Postmarketing Risk Management Plan

This section is not applicable since the Applicant did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

As part of the Review Team's assessment of the drug-associated myopathy adverse event profile found in the safety evaluation, a formal consult was requested so that the reviewers and management in the Division of Anesthesia, Analgesia, & Rheumatology Products (DAARP) could comment on the findings. The formal consultation was accompanied by informal discussions between DAARP and the Review Team primarily regarding the safety implications and possible label language. The completed consult written by Dr. Keith Burkhart is included in the NDA Action Package and will be briefly summarized below.

The DAARP consultant concluded that:

- There is a strong association between LdT and elevations in CK levels and myopathy.
- Although the data from the sponsor's submission clearly demonstrates that a greater proportion of LdT-treated subjects developed CK elevations compared to LAM-treated subjects, it is difficult to explain the relatively similar development rate of myopathy symptoms. Although a slightly higher percentage of LdT subjects developed symptoms of myopathy it was not to the same degree that they developed elevations in CK levels. It is difficult to explain these results but it may relate to the underlying mechanisms whereby the drugs induce their muscle toxicity. Theoretically, patients with CK elevations may represent an at risk population. These patients may remain susceptible to an oxidant stress or other precipitating factor that when encountered may worsen mitochondrial toxicity and lead to myopathy.
- The term [redacted] should be removed from the proposed label language myopathy is a very broad term that encompasses the etiologies that may be responsible for the cases of elevated CKs and patients' symptoms. Secondly, the term [redacted] connotes a specific clinical disorder that requires specific therapy. From our reading of the case reports provided in your review there were no biopsy-confirmed cases of [redacted] (typically characterized by peri-fascicular or peri-vascular infiltrates of lymphs and/or neutrophils and/or eosinophils). Additionally, although there were a large proportion of subjects presenting with elevated CKs, only a minority of these subjects were symptomatic. It maybe of use to specifically state in the label the proportion of subjects presenting with an elevated CK compared to controls and what proportion of them developed clinical symptoms and how they responded after withdrawal of telbivudine. This will provide a treating physician with more data when deciding whether telbivudine should be stopped in a subject responding to the drug but who has developed elevated CKs with or without symptoms of a myopathy. Finally, consider noting that muscle pain may also include unexplained chest and abdominal pain. Otherwise, the DAARP consultant agreed with the Skeletal Muscle Warnings, proposed by DAVP, to be included in the label.
- We also agree that post-marketing studies should be performed that carefully evaluate outcomes in patients who develop CK elevations and symptoms of myopathy while

receiving treatment with LdT. Monitoring for predisposing and precipitating factors should be tracked through the case report forms. Consider defining a cohort of subjects who would have EMGs and possibly muscle biopsies performed to help understand the pathophysiology. Consider following all subjects for resolution of their myopathy to determine if some patients do suffer irreversible myopathic disease.

MO Comments
As recommended by the DAARP Consultant and as noted below in Section 9.3.1, Risk Management Activity, the Division will continue discussions with the Applicant to ensure that a standardized management approach is implemented for all of subjects who develop CK elevations and/or muscle-related symptoms in the ongoing and future LdT clinical studies. The development of a systematic approach, which is required by protocol, will enable the systematic collection of the same data across studies. This may allow better characterization of LdT-associated myopathy. These considerations may include a possible cohort of subjects with myopathy who would have EMGs and possibly muscle biopsies to help understand the pathophysiology.

Also, as recommended by the DAARP Consultatnt, the LdT label has been modified to incorporate more information on the proportion of subjects presenting with an elevated CK compared to controls and what proportion of them developed clinical symptoms and how they responded after withdrawal of LdT.

9. OVERALL ASSESSMENT

9.1 Conclusions

The FDA Clinical and Statistical Reviewers concluded that in a well-conducted, multinational, study in subjects with compensated liver function, LdT was safe and effective in the treatment of adults with chronic HBV infection and evidence of ongoing liver inflammation. The data collection, study cohorts, selection of endpoints, and efficacy and safety analyses were adequate and appropriate to make the conclusion that LdT is safe and effective when used for its indicated purpose over 52 weeks of dosing.

As noted in Dr. Fraser Smith's Statistical Review, the efficacy analyses revealed the following:

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

- LdT was non-inferior to LAM in both HBeAg subpopulations for ALT Normalization and Virologic Breakthrough at Week 48.[69]

- LdT was also non-inferior to LAM in the HBeAg-positive subpopulation for Virologic

[69] See Section 6.1.5, Clinical Microbiology for a discussion of the differences in virologic endpoints between those used by the Applicant and those used by the FDA Microbiology Reviewer analyses of virologic failure vs. treatment failure and virologic rebound vs. virologic breakthrough.

Response, HBeAg Seroconversion and HBeAg Loss.

- The study failed to demonstrate that LdT was non-inferior to lamivudine for change in Ishak Fibrosis Score in the HBeAg-positive subpopulation and the treatment difference was almost statistically significant in favor of LAM. Since LdT could not achieve non-inferiority among HBeAg-positive LdT subjects for the Change in Ishak fibrosis score, LdT could also not achieve non-inferiority or superiority for the endpoints that followed in the hierarchical fixed hypothesis of testing (primary treatment failure, HBsAg loss, HBsAg seroconversion).

Despite the findings of superiority among HBeAg-positive subjects for the key endpoints, the FDA review does not support the Applicant's claim of superiority for the HBeAg-positive subpopulation for any endpoints if LdT was not superior to LAM for any previous endpoints in the hierarchy of fixed hypothesis testing. Findings of superiority in one HBeAg subpopulation (e.g. TR, Histologic Response, Serum HBV DNA Reduction, and Serum HBV DNA Undetectable) would have to be confirmed in a second study (or population) for a labeling claim of superiority to be valid.

Sensitivity analyses conducted by both the Applicant and the FDA Statistical Reviewer supported the robustness of these results. In addition, the treatment effect measured by the primary efficacy endpoint was not observed consistently across select populations within subgroups based on gender, race, age, geographic region, and a variety of baseline disease covariates as described above in the discussion of subgroup analyses for the primary efficacy endpoint within in Section 6.4, Efficacy Findings.

Any review of a drug's antiviral efficacy must include an understanding of the development of resistance to the drug. The applicant conducted extensive resistance testing of HBV isolates to LdT during the pivotal study. The major conclusions of the FDA virologists include several key points.

- Genotypic analyses at week 52 identified resistance-associated amino acid substitutions rtA181T and, rtM204I, alone or in combination with rtL80I/V, rtL180M, and/or rtL229W/V. These changes were detected in 48% (49/103) of the HBeAg-positive subjects and in 100% (12/12) of the HBeAg-negative subjects on LdT.
- Cross-resistance has been observed among HBV nucleoside analogues. In cell-based assays, LAM-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1000-fold reduced susceptibility to telbivudine. LdT retained wild-type phenotypic activity (1.2-fold reduction) against the LAM resistance-associated substitution rtM204V alone, but this substitution is unlikely to occur in isolation among LAM recipients. The efficacy of LdT against HBV harboring the rtM204V mutation has not been established in clinical trials.
- HBV encoding the ADV resistance-associated substitution rtA181V showed 3- to 5- fold reduced susceptibility to LdT in cell culture, while HBV encoding the ADV resistance-associated substitution rtN236T remained susceptible to telbivudine.

The findings suggest that LdT is unlikely to work in most subjects with LAM resistance (rtM204I or rtL180M/rtM204V). While LdT retained *in vitro* susceptibility to rtM204V alone, this mutation is not usually found in isolation among LAM-resistant patients. The findings also suggest that LdT is unlikely to be effective in subjects with ADV resistance (rtA181V) because LdT is 3 to 5 times less effective against this mutation, but clinical experience will reveal whether or not LdT may have a role for subjects with ADV resistance due to the rtN236T substitution. Since ETV-associated resistance substitutions have emerged when LAM-resistant mutations at L180 and/or M204 are

present. LdT is unlikely to retain efficacy among patients with ETV resistance because those patients will also have underlying LAM-resistant mutations.

Independent FDA review concluded that the safety profile of LdT was similar to that of LAM in the pivotal study. There were few differences in the pattern of AEs reported by LdT-treated patients compared to LAM-treated patients, with the notable exception of CK elevations and muscle-related weakness among LdT recipients. The pattern of commonly reported AEs was very similar in the LAM-refractory patients, with 75% of LdT subjects and 71% of LAM subjects reporting some AE. If all AEs of any intensity are considered, the most commonly reported events in LdT-treated subjects included: upper respiratory infection, fatigue/malaise, nasopharyngitis, headache, CPK increased, abdominal pain, and cough (see Table 7.1.5.4A). Many of these events are common in the general population and in the population of patients with chronic HBV. Because the pivotal study used LAM as the active control, it was somewhat difficult to determine true rates of LdT-related AEs. Even though the AE profile for LdT is similar to that of LAM does not mean that the AEs occurring in both treatment groups are not drug-related.

Four categories of adverse events deserve increased attention because of either the potential seriousness of the events or questionable signals from animal toxicology studies: acute exacerbations of hepatitis (ALT flares), neuropathic AEs, nephropathy, and CK elevations with myopathy and muscle weakness. To date, only CK elevations and myopathy with muscle weakness have been shown to occur more frequently among LdT-treated subjects compared to LAM-treated subjects.

During the LdT development program, ALT flares were tracked both during treatment and off-treatment follow-up. ALT flares were documented infrequently in subjects during the on-treatment period but occurred more often in subjects receiving LAM; 3% of LdT-treated subjects and 5% of LAM -treated subjects experienced a flare, based on AASLD flare criteria. ALT flares more commonly resulted in study drug discontinuation among LAM subjects than LdT subjects. There was very little limited data to estimate the risk of hepatitis B exacerbation after treatment discontinuation; however, the available data do suggest that persons who discontinue therapy may be at increased risk for post-treatment flares, relative to persons who start another form of anti-HBV treatment.

Because LdT-associated CK elevations were identified in the Phase 2b study and the pivotal trial, CK-related AEs were reviewed in detail for this review. In NV-02B-007, CK elevations occurred in both treatment arms; however median CK levels were higher in LdT-treated subjects by Week 52. Grade 1-4 CK elevations occurred in 72% of LdT-treated subjects and 42% of LAM-treated subjects, whereas Grade 3/4 CK elevations occurred in 9% of LdT-treated subjects and 3% of LAM-treated subjects. Most CK elevations were asymptomatic but the mean recovery time was longer for subjects on LdT than subjects on LAM. While there was not a uniform pattern with regard to the type of adverse event and timing with respect to the CK elevation, 8% of LdT-treated subjects with Grade 1-4 CK elevations experienced a CK-related adverse event[70] (within a 30-day window) compared to 6% of LAM-treated subjects. Furthermore, 9% (5/55) of the LdT-treated subjects with a CK-related adverse event interrupted or discontinued study drug to the adverse event; these subjects recovered after study drug discontinuation or interruption. Less than 1 % of LdT-subjects overall were diagnosed with myopathy, including muscle-weakness; those subjects

[70] Includes preferred terms: back pain, chest wall pain, non-cardiac chest pain, chest discomfort, flank pain, muscle cramp, muscular weakness, MSK pain, MSK chest pain, MSK discomfort, MSK stiffness, myalgia, myofascial pain syndrome, myopathy, myositis, neck pain, non-cardiac chest pain, and pain in extremity.

who discontinued study drug recovered. There have not been any known clinical cases of rhabdomyolysis, with or without renal failure, in the LdT development program.

There seems to be an emerging pattern of a infrequent, cumulative, toxicity resulting in myopathy, including muscle weakness, for subjects on LdT. The myopathy occurs with LdT use greater than 8-10 months. The possible mechanism of LdT muscle toxicity is unclear. There is also insufficient data to determine whether or not the subjects who developed drug-associated myopathy share a common predisposing risk factor. Additional information on subjects with this clinical presentation will collected in the ongoing LdT trials, to allow better characterization of this phenomenon.

High LdT doses led to some gastrointestinal (GI) intolerance in pregnant rabbits, non-pregnant monkeys, and rats. One pregnant rabbit died at the 1000 mg/kg/day dose, while two does had premature deliveries and one aborted. The animals showed evidence of gastrointestinal irritation, including reduced food consumption and less body weight gain, abnormal feces, erosion on the stomach mucosal surface, reddish fluid and appearance in the intestine, and distended stomach and intestine (with gas) leading the study director to attribute the negative pregnancy outcomes to maternal toxicity. The death of the pregnant rabbit occurred after more than 10 doses of LdT; hence GI irritation could be a dose limiting toxicity in rabbits. The AUC value in the pregnant rabbits at 1000 mg/kg/day was 2-3 times higher than those at the highest doses studied in mice, rats, and monkeys, and 37 times higher than that in humans. Despite this preclinical finding, the rate of occurrence of AEs in the Gastrointestinal Disorders SOC was equal between the treatment arms (30% LdT and 30% LAM). Only one subject in the pivotal trial discontinued LdT due to an AE in the Gastrointestinal Disorders SOC (nausea/loose stools) which resolved after study drug discontinuation. While this preclinical GI toxicity is concerning at very high LdT exposures, the AUC associated with this GI toxicity is 37-times higher than that in humans and is unlikely to be dose limiting in humans. It is unknown, however, whether or not patients with pre-existing gastrointestinal disease or patients who experience a significant LdT overdose may be at risk for more severe GI toxicities.

The preclinical findings of spinal cord and sciatic axonopathy were noted in all LdT dose groups (including controls) in monkeys suggesting that the findings are spurious. Nevertheless, sensory-related AEs were evaluated in the pivotal study and rates were similar across treatment groups. The proportion of subjects reporting any sensory symptom[71] was 3% for LdT-treated subjects and 2% for LAM-treated subjects; this difference is largely explained by the higher rate of dysgeusia among LdT-treated subjects. In short, there were no significant differences between the treatment arms. No significant pattern of LdT-related sensory AEs could be identified.

The highest LdT dose group among Sprague-Dawley rats had a higher rate of mortality due to chronic progressive nephropathy (CPN)[72], raising questions regarding the role of LdT in the development of this renal toxicity. In clinical studies with LdT, there was no evidence for a pattern of LdT-associated nephropathy in the Phase 1 and 2 trials or the Phase 3 registrational trial. Only one case of nephrotic syndrome in an LdT-treated subject has been reported and that subject had multiple pre-existing risk factors (diabetes mellitus, hypertension, baseline proteinuria). Based on current evidence, it seems unlikely that LdT worsens renal function in subjects with chronic

[71] Includes preferred terms: dysesthesia, dysgeusia, sensory loss, intercostal neuralgia, neuropathic pain, polyneuropathy, sciatica, sensation of heaviness, paraesthesia, hypoaesthesia, hypoaesthesia oral, paraesthesia oral, and neuralgia

[72] Chronic progressive nephropathy (CPN) occurs spontaneously and often in older Sprague-Dawley rats. There is no direct correlate for CPN among human renal diseases.

hepatitis B and normal renal function. It is possible, however, that as more subjects with chronic hepatitis B and compromised renal function or a high risk for compromised renal function (e.g diabetes, hypertension, elderly, etc.) initiate treatment with LdT, an adverse event profile of nephropathy may emerge.

9.2 Recommendation on Regulatory Action

This Medical Officer recommends the approval of telbivudine (LdT) for the treatment of chronic Hepatitis B Virus (HBV) in subjects with compensated liver disease and evidence of active liver inflammation by either elevated liver transaminases or liver biopsy. This recommendation is based on review of the efficacy and safety data submitted by Idenix Pharmaceuticals for this New Drug Application (NDA). There were not any significant inadequacies identified in the NDA that would prevent the approval of LdT.

Several issues have been considered in determining the overall risk-benefit of LdT in the treatment of chronic HBV and how LdT might fit into the current HBV treatment armamentarium. Chronic HBV contributes to the high rates of cirrhosis, hepato-cellular carcinoma (HCC), and mortality worldwide. Among subjects receiving study drug for 52 weeks in the pivotal, Phase 3 registrational trial, NV-02B-007, LdT use resulted in reliable drug exposure in human subjects, no known significant drug-drug interactions, normalization of liver enzymes, reduced HBV viral load, and improvement in liver histology, that was approximately equivalent to that achieved with administration of lamivudine (LAM). Notably, LdT was non-inferior to LAM in the achievement of the primary efficacy endpoint, Therapeutic Response, and the principal secondary efficacy endpoint, Histologic Response, among both HBeAg-positive and HBeAg-negative nucleoside-naïve subjects with chronic compensated HBV. For the primary efficacy endpoint, Therapeutic Response, LdT was non-inferior to LAM in Asians and Other Races in both HBeAg subpopulations and Caucasians who were HBeAg-Negative. There were few non-Asians and non-Caucasians in the pivotal trial, however, limiting this Reviewer's ability to interpret treatment effects that might possibly be linked to ethnicity. The Applicant will be asked to conduct an additional safety and efficacy study among select racial/ethnic groups (African-Americans and Hispanics) that were underrepresented in the pivotal trial.

The general tolerability and safety profile of LdT was similar to that of LAM over the observation period in the clinical trial, with the exception of a higher rate of CK elevations and the occurrence of an infrequent, but significant drug-associated myopathy with muscle weakness. Assessment of the drug's safety, tolerability, and efficacy in dosing beyond 52 weeks is ongoing.

These findings from the LdT studies must be weighed against findings that are less clearly understood. LdT was unable to achieve non-inferiority when compared to LAM for HBeAg-positive subjects for the secondary efficacy endpoint of Change in Ishak Fibrosis Score. The measured impact of LdT on disease progression, as measured by fibrosis, should be tempered by the impact of LdT on other markers of clinical HBV outcomes, including TR and histologic response, where LdT met non-inferiority criteria and the limitations of liver biopsy.

Uncertainty also emerges in the assessment of the potential risk that LdT may cause a significant myopathy with associated muscle weakness in a subset of subjects. The features that increase risk for the development of this adverse event are not understood. Data derived from ongoing studies are expected to provide more information. Skeletal muscle warnings were agreed upon by the FDA and the Applicant and have been included in the LdT label.

According to the clinical pharmacology findings reviewed by the FDA, after a radioactive oral 600mg dose of LdT, 91.6% of total dose was recovered in the urine (41.9%) and feces (49.6%) within 168 hours of dosing. LdT was excreted primarily in urine by passive diffusion, resulting in a low likelihood for interaction between LdT and other renally-excreted drugs. In addition, recommendations for dosing in renal failure were derived from clinical pharmacology studies of LdT among subjects with renal impairment. Dose adjustment was not found to be necessary among subjects with hepatic impairment.

In conclusion, the Phase 2 and Phase 3 LdT development program provided enough information on which to establish dose recommendation of 600mg once daily for nucleoside-naive adults with chronic hepatitis B, evidence of active liver inflammation by either elevated liver transaminases or liver biopsy, and compensated liver disease.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Applicant did not submit a formal risk management plan, however, the following risk management activities planned for LdT after approval:

- As a required Phase 4, post-marketing commitment, the Applicant has agreed to submit the 104-Week data for their pivotal Phase 3 trial, NV-02B-007. These results will provide more safety data for analysis of existing or future LdT-associated toxicities.
- The Applicant will also submit periodic safety reports for review.
- The label includes Warnings language regarding the risk of lactic acidosis, hepatic steatosis, Hepatitis B exacerbation post-discontinuation of therapy, and drug-associated myopathy in an effort to minimize the risk/benefit ratio associated with the use of this product.
- The label contains a number of usage statements to assist healthcare providers in how, when and in whom to use this product.
- The Division will continue discussions with the Applicant to ensure that a standardized management approach is implemented for all of subjects who develop CK elevations and/or muscle-related symptoms in the ongoing and future LdT clinical studies. The development of a systematic approach, which will be required by protocol, will better enable the systematic collection of the same categories of information across studies to allow better characterization of LdT-associated myopathy. The Applicant has agreed and is planning to solicit feedback from several experts with the necessary background and expertise to develop the most medically appropriate algorithm and/or approach.
    - This approach should include a protocol-specified definition for the types of clinical scenarios (e.g. CK elevation of any level with muscle weakness) that should trigger a specific algorithm for clinical, laboratory and other analyses.
    - The algorithm should outline specific approaches based on symptom presentation (e.g. subjects with CK elevations and fatigue should not necessarily get a muscle biopsy) and may include full musculoskeletal exam including strength testing, urine myoglobin, CK, CK fractionation, EMG, muscle biopsy, etc.

Also, the Office of Drug Safety (ODS) has been briefed regarding the safety issues with this NDA submission at an NDA Safety Meeting held on September 25, 2006. If there are new or increased post-marketing safety signals, ODS will be consulted formally.

9.3.2 Required Phase 4 Commitments

The Applicant has agreed to a number of post-marketing commitments designed to provide additional information on the durability of response to LdT treatment, efficacy, and safety in additional key subject populations.

During a labeling teleconference on October 12, 2006, the Applicant was notified that this NDA, as an application for a new molecular entity, would be required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. In the original NDA submission, the Applicant proposed a general pediatric development plan and requested a parital waiver for conducting pediatric studies in the neonatal age group (ages 0 through 2 years). The Division is not granting a waiver for any pediatric studies at this time. The Applicant understands that the deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) will be outlined in a Written Request for pediatric exclusivity subsequent to the action date for this NDA submission and will be considered required postmarketing study commitments.

Under the Pediatric Research Equity Act (PREA), the Division of Antiviral Products (DAVP) is deferring the following pediatric studies of LdT:

1. Deferred pediatric study/substudy under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.

2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 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.

The additional required Phase 4 commitments are described below:

Clinical

1. Complete and submit the final study report for Study NV-02B-007, the 104-Week, Phase 3 registrational trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with HBeAg-positive and HBeAg-negative chronic hepatitis B and compensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: July 2007

2. Conduct and submit a final study report to evaluate the use of LdT in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (blacks/African Americans, Hispanics).

   Protocol submission: June, 2007
   Final report submission: June 2010

3. Conduct and submit a final study report for an efficacy and safety study of telbivudine in subjects who are coinfected with HIV and HBV. This study should include analysis of virologic, biochemical, and serologic endpoints for both HIV and HBV. It should also include evaluation of safety, and evaluation of HBV and HIV resistance.

   Protocol submission: June, 2007
   Final report submission: June 2010

4. Complete and submit the final study report for Study NV-02B-011, the double-blind trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with chronic hepatitis B and decompensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: April 2010

5. Complete and submit the final study report for Study NV-02B-018, the open-label trial comparing the efficacy and safety of telbivudine to adefovir dipivoxil in subjects with HBeAg-positive compensated chronic hepatitis B.

   Protocol submission: Study Ongoing
   Final report submission: June 2007

6. Complete and submit the final study report for Study NV-02B-022, the open-label, non-comparative trial assessing the long-term antiviral efficacy and safety of telbivudine in subjects with HBeAg-positive and HBeAg-negative compensated and decompensated chronic hepatitis B that have been previously treated in Idenix-sponsored telbivudine studies.

   Protocol submission: Study Ongoing
   Final report submission: May 2012

Clinical Pharmacology

7. Conduct and submit a final study report for a study evaluating CYP induction potential for telbivudine using in vitro or in vivo studies.

   Protocol submission: January 2007
   Final report submission: January 2008

8. Conduct and submit a final study report(s) for in vitro studies to evaluate if telbivudine is a P-gp inhibitor.

   Protocol submission: January 2007

Final report submission: January 2008

Microbiology

9. Conduct and submit a final study report for a study to determine the anti-HBV cell culture combination activity relationships of telbivudine with entecavir.

   Protocol submission: December 2006
   Final report submission: April 2007

10. Conduct and submit a final study report for a study to determine the anti-HBV combination activity relationships of telbivudine in cell culture with the HIV NRTIs abacavir, emtricitabine, lamivudine, tenofovir, zalcitibine, and zidovudine.

    Protocol submission: February 2007
    Final report submission: November 2007

11. Conduct and submit a final study report for a study to determine the susceptibility to telbivudine and adefovir of the HBV rtA181 variants, rtA181T and rtA181S.

    Protocol submission: Study Ongoing
    Final report submission: November 2007

12. Conduct and submit a final study report for a study to determine the susceptibility in cell culture of HBV harboring the following mutations of highly conserved amino acid residues among HBV isolates: R22C, W58G, L69P, L82M, P99L, L180M, L209V, T240I, I254F, P261L, G295E, A307V, L331F, or A342T. These amino acid substitutions were found in the viruses of patients who experienced virologic failure (serum HBV DNA levels ≥1,000 copies/mL at Week 52) to telbivudine therapy.

    Protocol submission: February 2007
    Final report submission: February 2008 and December 2009

13. Conduct and submit a final study report for a study to determine the mitochondrial toxicity of telbivudine in growing muscle cells, cell lines and primary cells, and primary hepatocytes with appropriate controls to validate the results.

    Protocol submission: March 2007
    Final report submission: March 2008

14. Complete and submit a final study report for ongoing genotypic and phenotypic analyses of HBV DNA from patients who experience virologic failure to long-term telbivudine therapy (serum HBV DNA levels ≥1,000 copies/mL) in ongoing clinical trials.

    Protocol submission: Study Ongoing (NV-02B-007)
    Final report submission: July 2007 update for NV-02B-007 and then annually for Those NV-02B-007 patients who roll-over to NV-02B-022 (July 2008 and July 2009).

9.3.3 Other Phase 4 Requests

There are no additional recommended or optional post-marketing commitments.

9.4 Labeling Review

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Medical- 1

A copy of the full DMETS consult is included in the NDA Action Package.

The Patient Package Insert (PPI) was submitted to the Division of Surveillance, Research and Communication Support (DSRCS) for review and approved. The PPI includes information about ALT flares, lactic acidosis and muscle-related symptoms.

A copy of the DSRCS consult is included in the NDA Action Package.

9.5 Comments to Applicant

At this time, all comments pertinent to LdT labeling and Phase 4 commitments forwarded to the Applicant are described in Sections 9.3 and 9.4 above. No other comments need be conveyed to the Applicant.

10. APPENDICES

10.1 Review of Individual Study Reports

Information from relevant individual studies was interspersed throughout the review.

10.2 Line-by-Line Labeling Review

Please refer to Section 9.4 for discussion of clinical aspects of the labeling review.

REFERENCES

Please refer to footnotes included throughout the review

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/s/

Charlene Brown
10/25/2006 12:01:53 PM
MEDICAL OFFICER

Kathrine Laessig
10/25/2006 12:04:39 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10-25-06

FROM: Debra Birnkrant, M.D.
Director, Division of Antiviral Products
Office of Antimicrobial Products

TO: Division File

SUBJECT: Division Director's Memorandum for New Drug Application (NDA) 22-011 for telbivudine 600 mg tablets for the treatment of chronic hepatitis B infection

1.0 Background

On December 30, 2005, Idenix Pharmaceuticals, Inc. (Idenix) submitted NDA 22-011 for telbivudine 600 mg tablets for treatment of chronic hepatitis B virus (HBV) infection. The NDA for telbivudine was not presented to the Antiviral Drugs Advisory Committee because the Division felt that non-inferiority was clearly established and safety was comparable to lamivudine, the control in the principal trial, although there is an emerging signal of myopathy with this new chemical entity.

This memorandum summarizes the findings in the NDA and is written in support of approval of this application.

2.0 Dose Finding

Dosage selection was rational and based on review of data from a phase 1/2a dose-finding trial, 001 that predicted the maximal achievable antiviral efficacy between 400-800 mg per day. Further data from trial 003 indicated that 400 mg and 600 mg were also similar in efficacy. However, a dose of 600 mg was chosen for the phase 3 trial based on an E_{max} model and the previously mentioned trials to balance efficacy, emergence of resistance and safety. For a detailed clinical pharmacology review, please see comments by Dr. Jenny Zheng.

3.0 Efficacy results

The efficacy of telbivudine was demonstrated in a large phase 3 trial, the Globe study (study 007) in which nucleoside naïve, e antigen positive subjects and e antigen negative subjects were randomized in a 1:1 ratio to receive either telbivudine 600 mg or lamivudine 100 mg daily. Although the Globe study was a single study, it was designed so that each patient group would be analyzed separately and is consistent with regulatory guidance regarding the use of a single study for registration. Specifically the study was multicenter, incorporated a type-one error of <0.001, studied a range of chronic hepatitis B baseline characteristics, and evaluated multiple endpoints (virologic, serologic, histologic and changes in transaminases), which were all concordant.

The primary efficacy endpoint was therapeutic response defined as loss of e antigen or ALT normalization and serum HBV DNA < 10^5 copies/mL by the COBAS Amplicor PCR assay. This was a new primary composite endpoint designed to detect virologic and biochemical response, however histology at 52 weeks was a key secondary endpoint obtained in a majority of subjects. Previous trials of other approved therapies for treatment of chronic hepatitis B infection have used histology as the primary endpoint. It was agreed that therapeutic response would be the primary endpoint as long as histology was obtained in an adequate number of participants. Although the Division permitted Idenix to designate therapeutic response as the primary protocol endpoint, prior to the conduct of this study the Division made clear to Idenix that noninferiority for histologic improvement was a non-negotiable criterion for approval and would be highlighted in product labeling. For histologic improvement, multiple studies allow the selection of an adequate noninferiority margin when comparing other hepatitis B treatments to lamivudine. In three studies comparing lamivudine to placebo, the difference in point estimates for histologic improvement was 30% in every study. In addition, when adefovir was compared to placebo the difference in point estimate for histologic improvement was approximately 30% in two studies. The margin of efficacy for chronic hepatitis B drugs compared to placebo has been large, remarkably reproducible and unambiguous. Therefore, a noninferiority margin of -15% is unequivocally justified.

Other secondary endpoints were multiple and included: serum HBV DNA reduction, serum HBV DNA undetectable (<300 copies/mL), ALT normalization and virologic breakthrough at week 48.

In the primary efficacy analysis non-inferiority had to be demonstrated first before testing for superiority. Also, there were hierarchical methods with regard to determining the significance of the endpoints explained as follows: the applicant

could not claim superiority for any secondary endpoints in the hierarchy if telbivudine was not superior to lamivudine for any previous endpoints. These findings are summarized in the medical officer review by Dr. Charlene Brown and the statistical review by Dr. Fraser Smith. Of note, the non-inferiority margin for the composite therapeutic response endpoint was estimated at 15% based on the following: the applicant's best estimate of response rates for therapeutic response for telbivudine was 50% and that for placebo at 10%. Half of the distance between these two assumptions is 20%, therefore the delta was conservatively proposed at 15%. Further, if the lower boundary of the confidence interval was above -15%, then non-inferiority was claimed and if the lower boundary was above 0, then superiority was claimed.

Briefly, based on the aforementioned hierarchical testing procedure, telbivudine was superior to lamivudine in the e antigen positive population and non-inferior to lamivudine in the e antigen negative population for the following endpoints: therapeutic response (75% vs. 67% for e antigen positive, telbivudine compared to lamivudine and 75% vs. 77% for the e antigen negative population, telbivudine compared to lamivudine), histologic response (69% improvement vs. 60% improvement for telbivudine compared to lamivudine for e antigen positive subjects and 69% vs. 68% for telbivudine compared to lamivudine for e antigen negative subjects), serum HBV DNA reduction (mean reduction from baseline=6.4 $\log_{10}$ copies/mL vs. 5.5 $\log_{10}$ copies/mL for telbivudine compared to lamivudine in e antigen positive patients and 5.2 $\log_{10}$ copies/mL vs. 4.4 $\log_{10}$ copies/mL for telbivudine compared to lamivudine in e antigen negative patients) and serum HBV DNA undetectable (60% vs. 40% for telbivudine compared to lamivudine for e antigen positive subjects and 88% vs. 71% telbivudine compared to lamivudine for the e antigen negative subjects). Telbivudine was non-inferior to lamivudine for both e antigen populations for ALT normalization, and virologic breakthrough at week 48. Telbivudine was also non-inferior to lamivudine in the e antigen positive population for virologic response, e antigen seroconversion and e antigen loss. The Globe study failed to demonstrate that telbivudine was non-inferior to lamivudine for change in Ishak Fibrosis Score in the e antigen positive population; this finding is likely within the histologic sampling error. Further, change in fibrosis may take longer than one year in order to see positive results.

Overall, the Division did not allow Idenix to claim superiority of telbivudine over lamivudine for therapeutic response, histologic response, serum HBV DNA reduction and serum HBV DNA undetectable endpoints within the e antigen positive population without replication in a second clinical trial.

The Globe study will continue for a second year and the applicant is being requested to conduct an additional trial in minority racial and ethnic groups who were under-represented in the principal trial. In addition the applicant is being requested to conduct a trial in co-infected subjects, those with decompensated

liver disease, and a comparative study examining adefovir vs. telbivudine in compensated subjects.

4.0 Summary of Safety

The safety of telbivudine was demonstrated in the Globe study comprising 1,367 nucleoside naïve subjects who received telbivudine (n=680) and lamivudine (n=687), in addition to supporting studies. In general, the adverse event profile of telbivudine was similar to lamivudine. Regarding safety, three areas are worth noting: resistance development, hepatic flares, and myopathy.

Per Dr. Sung Rhee's virology review, there is significant cross resistance between telbivudine and lamivudine. Telbivudine was inactive against lamivudine-resistant strains encoding either the M204I substitution or the L180M/M204V substitutions. Telbivudine exhibited little-to-no loss of anti-HBV activity in cell culture against the less frequent M204V mutation, but efficacy has not been established in this population. The adefovir-resistance associated substitution, A181V showed a 3-5 fold decrease in cell culture susceptibility to telbivudine while the N236T substitution remained susceptible. Also see post-marketing commitments.

The second safety issue of hepatic flares is worthy of comment. Class labeling related to hepatic flares appears in a box warning as with other nucleosides for this indication. Briefly, on-treatment flares occurred more frequently with lamivudine as compared to telbivudine at a rate of 5.1% and 3.2 %, respectively. The occurrence of ALT flares was more common in e antigen positive subjects. Periodic monitoring of hepatic function is recommended in labeling. The labeling also states that there are insufficient data on post-treatment ALT flares after discontinuation of telbivudine treatment.

Creatine kinase (CK) elevations were more frequent in the telbivudine arm as compared to lamivudine. Per Dr. Brown's review and as stated in the label, Grade 1-4 CK elevations occurred in 72% of telbivudine-treated subjects as compared to 42% in lamivudine-treated subjects. Grade 3-4 CK elevations were much less frequent but were also more common in the telbivudine arm compared to lamivudine, 9% vs. 3 %, respectively. Most CK elevations were asymptomatic, however 3/680 subjects on telbivudine were diagnosed with myopathy with muscular weakness. These three subjects recovered after telbivudine was discontinued. No cases of rhabdomyolysis were seen. Information about CK elevations and myopathy have been placed in the warnings section of the label. Upon review of pre-clinical data to asses this finding, telbivudine did not inhibit biochemical assays of human cellular DNA polymerases including mitochondrial DNA polymerase γ, and was not cytotoxic to dividing cells.

It is likely that cases of CK elevation with or without myopathy will be reported in ongoing clinical trials and post-marketing. Our Office of Surveillance and Epidemiology has been alerted to this possibility. At present, it is unclear how to monitor for this event because there has not been a clear pattern with regard to timing or degree of CK elevations. To examine this phenomenon more closely, ongoing trials will be amended to systematically assess CK elevations and the risk of myopathy. At present, based on available data, practitioners should interrupt dosing with telbivudine if myopathy is suspected and discontinue telbivudine if myopathy is diagnosed. Patients will need to be monitored for hepatic flares if telbivudine is discontinued.

5.0 Deaths

A total of 13 deaths occurred in the telbivudine development program. The reviewing medical officer agreed with the applicant's assessment regarding causality of all of the deaths. There was only one death in the Globe study. Subject # 118-013 who was receiving lamivudine died in a motor vehicle accident and his death was not attributed to study drug. One death, patient # 008-022 in study 015 died of hepatic failure while receiving lamivudine; this particular event was considered possibly related to study medication. Other causes of death included infections and complications of advanced liver disease.

5.0 Summary of Regulatory Issues

The following phase 4 commitments will be requested of the applicant:

Clinical

1. Complete and submit the final study report for Study NV-02B-007, the 104-Week, Phase 3 registrational trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with HBeAg-positive and HBeAg-negative chronic hepatitis B and compensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: July 2007

2. Conduct and submit a final study report to evaluate the use of telbivudine in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (blacks/African Americans, Hispanics).

   Protocol submission: June, 2007
   Final report submission: June 2010

3. Conduct and submit a final study report for an efficacy and safety study of telbivudine in subjects who are coinfected with HIV and HBV. This study should include analysis of virologic, biochemical, and serologic endpoints for both HIV and HBV. It should also include evaluation of safety, and evaluation of HBV and HIV resistance.

   Protocol submission: June, 2007
   Final report submission: June 2010

4. Complete and submit the final study report for Study NV-02B-011, the double-blind trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with chronic hepatitis B and decompensated liver disease.

   Protocol submission: Study Ongoing
   Final report submission: April 2010

5. Complete and submit the final study report for Study NV-02B-018, the open-label trial comparing the efficacy and safety of telbivudine to adefovir dipivoxil in subjects with HBeAg-positive compensated chronic hepatitis B.

   Protocol submission: Study Ongoing
   Final report submission: June 2007

6. Complete and submit the final study report for Study NV-02B-022, the open-label, non-comparative trial assessing the long-term antiviral efficacy and safety of telbivudine in subjects with HBeAg-positive and HBeAg-negative compensated and decompensated chronic hepatitis B that have been previously treated in Idenix-sponsored telbivudine studies.

   Protocol submission: Study Ongoing
   Final report submission: May 2012

Clinical Pharmacology

7. Conduct and submit a final study report for a study evaluating CYP induction potential for telbivudine using in vitro or in vivo studies.

   Protocol submission: January 2007
   Final report submission: January 2008

8. Conduct and submit a final study report(s) for in vitro studies to evaluate if telbivudine is a P-gp inhibitor.

Protocol submission: January 2007
Final report submission: January 2008

Microbiology

9. Conduct and submit a final study report for a study to determine the anti-HBV cell culture combination activity relationships of telbivudine with entecavir.

Protocol submission: December 2006
Final report submission: April 2007

10. Conduct and submit a final study report for a study to determine the anti-HBV combination activity relationships of telbivudine in cell culture with the HIV NRTIs abacavir, emtricitabine, lamivudine, tenofovir, zalcitibine, and zidovudine.

Protocol submission: February 2007
Final report submission: November 2007

11. Conduct and submit a final study report for a study to determine the susceptibility to telbivudine and adefovir of the HBV rtA181 variants, rtA181T and rtA181S.

Protocol submission: Study Ongoing
Final report submission: November 2007

12. Conduct and submit a final study report for a study to determine the susceptibility in cell culture of HBV harboring the following mutations of highly conserved amino acid residues among HBV isolates: R22C, W58G, L69P, L82M, P99L, L180M, L209V, T240I, I254F, P261L, G295E, A307V, L331F, or A342T. These amino acid substitutions were found in the viruses of patients who experienced virologic failure (serum HBV DNA levels ≥1,000 copies/mL at Week 52) to telbivudine therapy.

Protocol submission: February 2007
Final report submission: February 2008 and December 2009

13. Conduct and submit a final study report for a study to determine the mitochondrial toxicity of telbivudine in growing muscle cells, cell lines and primary cells, and primary hepatocytes with appropriate controls to validate the results.

    Protocol submission: March 2007
    Final report submission: March 2008

14. Complete and submit a final study report for ongoing genotypic and phenotypic analyses of HBV DNA from patients who experience virologic failure to long-term telbivudine therapy (serum HBV DNA levels ≥1,000 copies/mL) in ongoing clinical trials.

    Protocol submission: Study Ongoing (NV-02B-007)
    Final report submission: July 2007 update for NV-02B-007 and then annually for those NV-02B-007 patients who roll-over to NV-02B-022 (July 2008 and July 2009).

Pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required post marketing study commitments. Lastly, Indenix has joined the Antiretroviral Pregnancy Registry; the Registry is intended to provide an early signal of potential risks.

6.0 Regulatory Recommendation

Telbivudine will provide another treatment in the armamentarium of therapies for chronic hepatitis B infection and will be indicated for a broad patient population.

I concur with the findings of the multidisciplinary review team that the NDA for telbivudine should be approved. This determination was based on a review of the safety and efficacy data contained in the application. Non-inferiority of telbivudine compared to lamivudine was demonstrated and the indication for this new therapy is supported.

Phase 4 commitments will help to answer how telbivudine should be used in other populations, such as co-infected subjects. Resistance development including cross resistance will be further examined. Finally, safety issues related to CK elevations will continue to be explored.

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/s/

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MEDICAL OFFICER

Jeffrey Murray
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 10-13-06

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Products

TO: Division File

SUBJECT: Medical Team Leader Memo for NDA 22-011, telbivudine 600 mg tablets (tradename TYZEKA)

1.0 Background

TYZEKA is the tradename for telbivudine (LdT), a synthetic nucleoside analogue with selective antiviral activity against hepatitis B virus (HBV). LdT is phosphorylated intracellularly and the resultant LdT-triphosphate inhibits HBV DNA polymerase by competing with the natural substrate, deoxythymidine-triphosphate. Incorporation of LdT-triphosphate into viral DNA results in chain termination and inhibition of viral replication. The applicant, Idenix Pharmaceuticals, Inc. (Idenix) has submitted NDA 22-011 in support of 600 mg tablets of LdT. The applicant has proposed a dose of 600 mg once daily for treatment naïve patients. The requested indication is treatment of chronic hepatitis B in adults with evidence of active viral replication, persistently elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, or evidence of histologically active liver disease.

There are five therapeutic agents approved for the treatment of chronic hepatitis B. The first 3 are drug products, lamivudine (LAM), adefovir dipivoxil (ADV), and entecavir (ETV), and the second 2 are biologic products, interferon alfa-2b (IFN) and pegylated interferon alfa-2a (PEG-IFN). Although LAM has a very good tolerability profile, its utility is limited by the emergence of resistance in up to 25% of patients at one year and up to 75-80% of patients by 4 years. Generally, once resistant viral variants are present, patients experience a recrudescence of hepatitis with increasing viral loads, increased transaminase levels, and an increase in active liver disease as seen histopathologically. Adefovir has activity in LAM resistant patients; however its use is limited by nephrotoxicity in more advanced liver disease subjects. The approved dose of ADV is 10 mg once

daily, although 30 mg was found to be more efficacious in one of the pivotal trials; the higher dose resulted in a greater incidence of nephrotoxic adverse events. Entecavir was demonstrated to be superior to LAM for a number of endpoints in 3 registrational trials, however was found to be a carcinogen in animal testing. The fourth agent, IFN, must be administered parenterally for 6 months, and many patients experience significant tolerability problems often requiring treatment discontinuation. Although PEG-IFN requires less frequent dosing than IFN, it is similarly difficult to tolerate. The availability of new drug product for this serious and life-threatening disease provides patients with another option in therapy.

For more detailed discussions of the safety and efficacy data, please refer to the clinical review of Dr. Charlene Brown, and the biometrics review of Dr. Fraser Smith.

2.0 Summary of Efficacy

The efficacy of LdT has been demonstrated in a single large pivotal trial: NV-02B-007, referred to as the 007 or GLOBE study, with supportive evidence derived from a number of phase 2 studies including NV-02B-001 and NV-02B-003. The GLOBE study is an ongoing double-blind, randomized, active controlled study of adults with compensated liver disease, detectable HBV DNA, and ALT levels that are mildly elevated. Lamivudine is the active comparator, administered at the approved dose of 100 mg once daily while LdT was dosed at 600 mg once daily. Both subjects with hepatitis B e antigen positivity (eAg+) and negativity (eAg-) were enrolled. Previous applications have conducted studies of these subjects separately, but for administrative purposes they were combined into one trial in this development program. Due to differences in the natural history of eAg+ and eAg- disease, subjects were stratified at baseline according to eAg status and efficacy analyses were performed for each group separately.

The primary efficacy endpoint used for this trial differed from that of previous registrational programs for hepatitis B products. Historically, improvement in liver biopsy has been the primary endpoint, however for this study it was the most important secondary endpoint. DAVP had an advisory committee meeting in August of 2002 to discuss the utility of nonhistologic endpoints as primary in pivotal trials for new antihepatitis B products. The committee recommended flexibility in choice of endpoints. Thus, the applicant proposed and DAVP agreed upon a primary endpoint of Therapeutic Response (TR) which is a composite endpoint. For the eAg+ subjects, TR was defined as loss of detectable serum HBeAg or ALT normalization, and HBV DNA $< 10^5$ log copies/mL by COBAS Amplicor assay. For the eAg- subjects, TR did not include the HBeAg component since subjects were eAg- at baseline. TR is believed to be clinically meaningful because the individual components are all parameters followed by treating providers to demonstrate treatment response. Although individually they

may not correlate well with histology, in general a positive treatment effect is found for all in the setting of potent antiviral therapy.

The primary efficacy analysis revealed that LdT was superior to LAM for most endpoints in the eAg+ population, except for the endpoints of eAg seroconversion and ALT normalization. LdT was not superior to LAM for most endpoints in the eAg- population, except for log change in HBV DNA and proportion undetectable. Since the finding of superiority to LAM in the eAg+ population has not yet been confirmed by other data, it will not be described in product labeling, although the point estimates for each will be displayed. The results of the primary and selected secondary efficacy results are described in the table below.

Table 1 Summary of Efficacy from Study 007

Endpoint	eAg+ subjects		eAg- subjects	
	LdT 600 mg (N=458)	LAM 100 mg (N=463)	LdT 600 mg (N=222)	LAM 100 mg (N=224)
Histologic Improvement	69%	60%	69%	68%
Therapeutic Response	75%	67%	75%	77%
HBV DNA <300 copies/ml	60%	40%	88%	71%
ALT < 1 X ULN	77%	75%	74%	79%
HBeAg seroconversion	22%	22%	N/A	N/A

Subgroup analyses based on gender, race, and HBV genotype revealed only that among the eAg+ subjects, Asians were more likely to achieve PCR nondetectability. Among eAg- patients, Asians were more likely to achieve a TR, PCR nondetectability, and ALT normalization. However, there were few non-Asians and non-Caucasians enrolled in the trial, which limits the assessment of ethnic-related treatment effects.

Additional supportive evidence for the antiviral activity of LdT is provided by study 003, a phase 2b study of 400 and 600 mg doses of LdT versus 100 mg of LAM vs. the combination of 400 or 600 mg of LdT plus 100 mg of LAM. Although not powered to provide evidence of differences, all LdT containing arms demonstrated a trend of decrease in HBV DNA compared to the LAM monotherapy arm.

Overall, the treatment effect of LdT was consistently demonstrated across different endpoints, and in different patient populations including both eAg+ and eAg- patients. A study in subjects with decompensated liver disease is still ongoing at the time of this review.

3.0 Summary of Safety

In general, LdT was well tolerated and the adverse event profile, numbers of SAEs and deaths, and frequency of laboratory abnormalities were not significantly dissimilar to that of LAM, with the exception of more frequent elevations in creatine phosphokinase (CK) among the LdT treated subjects.

Two areas of the safety review were of special interest. The first, as mentioned previously, is the more frequent development of CK elevations among the LdT treated subjects compared to the LAM treated subjects. Seventy-one percent of subjects in the LdT arm of 007 developed a new-onset, on-treatment CK elevation compared to 41% of subjects in the LAM arm. Of these, 9% of subjects in the LdT arm had a Grade 3-4 elevation in CK, compared to 3% of the LAM treated subjects. The CK elevations were primarily asymptomatic, and very few resulted in study drug discontinuation. In addition, there was not a difference between the 2 treatment groups in the frequency of muscle related AEs (10% for LdT vs. 9% for LAM), nor were there any cases of rhabdomyolysis.

However, during the course of the review and evaluation of the original NDA data, the 120-day safety update, and IND 15-day safety reports, there was found to be a greater number of subjects receiving LdT who discontinued study drug due to a musculoskeletal related AE. Two subjects had SAEs suggestive of muscle weakness and 3 had AEs resulting in study drug discontinuation or interruption due to a muscle-related AE associated with myopathy or muscle weakness. Only 1 LAM treated subject discontinued study drug for a similar type of event. Generally these events occurred after at least 6 months of LdT exposure, however there did not appear to be a correlation between magnitude of CK elevation and risk of developing a myopathy event. The applicant agreed that there appears to be a rare AE of myopathy associated with LdT therapy and agreed to a WARNING in the LdT package insert describing this phenomenon.

Despite the CK elevations and the rare myopathy events, LdT has a safety profile that is otherwise comparable to LAM. Therefore, the applicant has provided substantive evidence of the safety of the 600 mg dose of LdT.

4.0 Summary of Virology

Please see the review of Dr. Sung Rhee for complete details of the virologic and resistance findings for LdT. In brief, by Week 52, 145/430 (34%) and 19/227 (8%) of HBeAg-positive and HBeAg-negative telbivudine recipients, respectively, had evaluable HBV DNA (≥1,000 copies/mL). Genotypic analysis detected one or more amino acid substitutions associated with virologic failure (rtM204I, rtL80I/V, rtA181T, rtL180M, rtL229W/V) in 49 of 103 HBeAg-positive and 12 of 12 HBeAg-negative patients with amplifiable HBV DNA and ≥16 weeks of treatment. The rtM204I substitution was the most frequent mutation and was associated with virologic rebound (≥1 $\log_{10}$ increase above nadir) in 34 of 46 patients with this mutation.

In cell-based assays, lamivudine-resistant HBV strains containing either the rtM204I mutation or the rtL180M/rtM204V double mutation had ≥1,000-fold reduced susceptibility to telbivudine. Telbivudine retained wild-type phenotypic activity (1.2-fold reduction) against the lamivudine resistance-associated substitution rtM204V alone. The efficacy of telbivudine against HBV harboring the rtM204V mutation has not been established in clinical trials. However, there is likely to be at least partial cross-resistance between LdT and LAM resistant virus. The rtL180M is a mutation that has been previously noted to result in decreased phenotypic susceptibility to entecavir, and the rtA181T mutation is associated with resistance to adefovir. However, no clinical information is available regarding the treatment of subjects with LdT resistant viral strains with either adefovir or entecavir.

6.0 Recommendation

I concur with the findings and recommendations presented by the medical officer's review by Dr. Charlene Brown. At this time, the applicant has provided substantive evidence for the safety and efficacy of LdT 600 mg tablets for the treatment of adult patients with chronic hepatitis B. Therefore, this application should be approved.

Katherine A. Laessig, M.D.

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