2 Synopsis

Name of finished product: Telbivudine (SEBIVO®, TYZEKA®, LdT)

Name of active ingredient: Telbivudine (LdT)

Study Description

Title of study: A Randomized Trial of Switching Antiviral Therapy from Lamivudine to Telbivudine (LdT) versus Continued Lamivudine Treatment in Adults with Chronic Hepatitis B

Investigator(s): Rifaat Safadi, MD et al.

Study center(s): A total of 28 centers participated in this study. The geographic regions and the respective number of centers are as follows: Asia/Pacific (14), Europe (10), and North America (4).

Publication (reference): Not applicable

Study Methods

Study period:

First patient randomized: 21 February 2005

Last patient completed: 05-December-2006

Phase of development: IIIb

Objectives: The primary objective of this study was to assess antiviral efficacy (serum HBV DNA reductions) in adult hepatitis B patients randomly switched to telbivudine or continued on lamivudine treatment, after 3-12 months of previous treatment with lamivudine.

The secondary objectives of the study were (1) to compare clinical efficacy outcomes in hepatitis B patients randomly switched to telbivudine or continued on lamivudine treatment, after 3-12 months of previous treatment with lamivudine. The primary markers of clinical efficacy were serum ALT normalization and a composite serologic efficacy endpoint termed Therapeutic Response (HBV DNA <5 $\log_{10}$ copies/mL with HBeAg loss or ALT normalized). Additionally, the number of patients with HBV DNA PCR negative and HBeAg responses (HBeAg loss and seroconversion) were assessed in an exploratory fashion, in the patient subgroup who were HBeAg-seropositive at study entry, (2) to compare clinical and laboratory safety observations in hepatitis B patients randomly switched to telbivudine or continued on lamivudine treatment, after 3-12 months of previous treatment with lamivudine, (3) to characterize the frequency of viral breakthrough, and treatment emergent HBV viral genotypes associated with viral breakthrough, for lamivudine-treated patients switched to telbivudine compared to patients who continued lamivudine treatment.

Methodology and treatment duration: This was a Phase IIIb, randomized, double-blind, multicenter study of treatment with telbivudine β–L-2'deoxythymidine (LdT) versus continued treatment with lamivudine, in adult patients with compensated chronic hepatitis B, who previously received 3-12 months of lamivudine therapy.

Patients were randomly assigned (1:1) to telbivudine (LdT) 600 mg or lamivudine (Lam) (100 mg). Eligible patients were randomized to one of the treatment groups prior to the first dose of study medication.

Number of patients (planned and analyzed): A total of 248 adult patients with chronic hepatitis B with compensated liver disease who previously received 3-12 months of lamivudine treatment were randomized to received LdT (N = 126) or Lam (N = 122). Patients were stratified

to one of the four following strata based on the screening HBeAg status and duration of prior lamivudine treatment period:

- HBeAg negative and 12-24 weeks of prior lamivudine therapy
- HBeAg negative and 25-52 weeks of prior lamivudine therapy
- HBeAg positive and 12-24 weeks of prior lamivudine therapy
- HBeAg positive and 25-52 weeks of prior lamivudine therapy

Diagnosis and main criteria for inclusion:

The study enrolled men and women 18 to 70 years of age with documented compensated chronic hepatitis B. Patients enrolled in the study were to meet the following key inclusion criteria:

- Clinical history compatible with compensated chronic hepatitis B;
- Detectable serum HBsAg at the Screening visit;
- HBeAg seropositive or seronegative;
- History of evidence of chronic liver inflammation, documented by previous history of elevated serum ALT and/or AST levels (at least two elevated ALT or AST values spanning six months or more, documented in available records), and/or chronic liver inflammation documented on previous liver biopsy with available pathology report;
- Serum ALT level at Screen <10 x ULN;
- Serum HBV DNA >3$\log_{10}$ copies/mL by the COBAS Amplicor HBV PCR assay at the central study laboratory.
- Patient was currently receiving lamivudine treatment for his/her hepatitis B, and had received lamivudine continuously for a duration of at least 12 weeks (three months) and not more than one year (12 months). The start of lamivudine therapy must have been documented in the patient's available medical records, together with periodic clinical monitoring conducted since the start of lamivudine therapy.

Eligible patients could not:

- Have been pregnant or breastfeeding. Women of childbearing potential must have had a negative serum beta-human chorionic gonadotropin (β-HCG) at Screening.
- Have been of reproductive potential (men and women) and unwilling to use a double-barrier method of contraception;
- Have been co-infected with hepatitis C virus (HCV), hepatitis D virus (HDV), HIV-1 or HIV-2;
- Have previously received antiviral treatment for hepatitis B other than lamivudine in the preceding 12 months;
- Have received other systemic immunomodulatory treatment for HBV infection in the preceding 12 months;
- Have had a medical condition that required prolonged or frequent use of systemic acyclovir or famciclovir (e.g., for recurrent herpes virus infections, etc);
- Have had a history of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or other clinical signs of hepatic decompensation.
- Have had a history of HCC or findings suggestive of possible HCC, such as suspicious foci on imaging studies or elevated serum alpha-fetoprotein (AFP) levels. In patients with such findings, HCC should be ruled-out prior to randomization for the present study.
- Have been abusing alcohol or illicit drugs, or had a history of alcohol abuse or illicit substance abuse within the preceding two years;
- Have had a medical condition that required frequent or prolonged use of systemic corticosteroids (e.g., severe asthma, severe arthritis or autoimmune conditions, organ transplantation, adrenal insufficiency, etc);
- Have had one or more additional known primary or secondary causes of liver disease, other than hepatitis B. Gilbert's syndrome and Dubin-Johnson syndrome, two benign disorders

associated with low-grade hyberbilirubinemia, did not exclude patients from participation in this trial;

- Have had any other concurrent medical condition likely to preclude compliance with the schedule of evaluations in the protocol, or likely to confound the efficacy or safety observations of the study (e.g., concurrent malignancies, history of unstable angina, repeated myocardial infarction or congestive heart failure, renal insufficiency, uncontrolled asthma or diabetes, unstable thyroid disease or other significant hormonal conditions, uncontrolled seizure disorders, severe psychiatric disorders, active tuberculosis under current treatment, etc.). A history of treated malignancy (other than hepatocellular carcinoma) was allowable if the patient's malignancy had been in complete remission off chemotherapy and without additional surgical interventions during the preceding three years;
- Have had a history of clinical pancreatitis.
- Have been enrolled or planned to enroll in another clinical trial of an investigational agent while participating in this study;
- Have had any of the following laboratory values at Screening:
  - Hemoglobin <11 g/dL for men or <10 g/dL for women [Female <100 g/L; Male <110 g/L;
  - Total white blood cell (WBC) <3,000/ mm^3;
  - Absolute neutrophil count (ANC) <1,500/mm^3 [<1.50 x 10^9/L];
  - Platelet count <75,000/mm^3 [<75 x 109/L];
  - Serum albumin <3.3 g/dL [<33g/L];
  - Total bilirubin ≥2.0 mg/dl [≥34µmol/L];
  - Serum creatinine ≥1.5 mg/dl [≥133µmol/L];
  - AFP >50 ng/mL [>50 µg/L] (requires further evaluation, to rule-out hepatocellular carcinoma);
  - Prothrombin time prolonged by more than 3 seconds, (based on the ULN of the reference value) despite vitamin K administration.

Test product and reference therapy – dose, dosage form, administration mode, batch numbers:

Study drugs were self-administered by patients orally, once daily for 52 weeks. Patients received 600 mg of telbivudine daily for 52 weeks or 100 mg of lamivudine daily for 52 weeks. Dosage modifications were not permitted in the study. The lot numbers of telbivudine and lamivudine dispensed during the 52-week treatment periods are listed below:

Drug product	Bulk Lot numbers	Bottled Lot numbers
Telbivudine	X0590204, X1890504, X3441104	178540, 192461, 203445
Telbivudine Placebo	X2190803, X0560204, X2450804	171860, 184841, 198115
Lamivudine	X1020504, X2500804, X3331104	176407, 188526, 203494
Lamivudine Placebo	X3051203, X1010504, X3801104	167054, 176401, 203496

Source: [Appendix 16.1.6]

Criteria for evaluation

Efficacy: The primary efficacy endpoint for the study was the reduction in serum HBV DNA concentration (log_{10} copies/mL) from Baseline to Week 24 for telbivudine-treated vs. lamivudine-treated patients.

Comparison in the change from Baseline to Week 52 in serum HBV DNA concentration was also assessed.

Secondary efficacy endpoints included serum HBV DNA suppression, maintained serum HBV DNA suppression, HBV DNA undetectable (PCR negative), maintained HBV DNA undetectable, ALT normalized, ALT normalization, maintained ALT normalization, composite serologic response, HBeAg loss, maintained HBeAg loss, HBeAg seroconversion, maintained HBeAg seroconversion, virologic response, maintained virologic response, HBsAg loss, HBsAg seroconversion, therapeutic response, maintained therapeutic response, treatment failure, and virologic breakthrough.

Safety: Safety was assessed by collection of information regarding all adverse events (AEs) and serious adverse events (SAEs), with assessment of their severity and relationship to study drug. Patients underwent assessments of vital signs, physical condition, and body weight, collection of blood samples for monitoring hematology and liver function, collection of urine for monitoring renal function, monitoring of vital signs, and physical examinations.

Bioanalytics: No pharmacokinetic analyses were performed during the study.

Statistical methods: Two analysis populations were defined for this study. The Intent-to-Treat (ITT) population included all patients who were randomized and received at least one dose of study medication with at least one post-Baseline observation. For all ITT analyses, patients were analyzed according to the treatment to which they were randomized. Patients who took other anti-HBV medications during the trial were included in the ITT population, but to avoid confounding the efficacy assessments, their efficacy observations were censored at the date of first dose of the prohibited anti-HBV medication.

The Safety population consisted of all patients who received at least one dose of study medication with a least one post-Baseline observation. For all analyses based on the Safety population, patients were analyzed according to the treatment actually received.

All efficacy analyses were based on the ITT population and were presented based on randomized treatment group. The last observation carried forward (LOCF) method was used for missing data for efficacy analyses.

The primary efficacy analysis was the reduction in serum HBV DNA concentration (log_{10} copies/mL) from Baseline assessed at Week 24 (using LOCF imputation for missing data). The null hypothesis was that there was no difference between the telbivudine and lamivudine treatment groups. This hypothesis was to be assessed using an Analysis of Covariance (ANCOVA) model with effects for Baseline stratification factors (HBeAg negative vs positive status, 12-24 vs 25-52 weeks of prior lamivudine therapy), geographic region, gender, age, race, Baseline serum HBV DNA, and Screening ALT. Interaction terms for treatment by HBeAg status (negative vs positive status) and treatment by length of prior lamivudine treatment (12-24 vs 25-52 weeks) were to be included in the model to examine the homogeneity of treatment effects. The Baseline stratification factors were to be constrained to stay in the model; non-significant covariates with p-values >0.1 were to be excluded from the final model.

Descriptive statistics for serum HBV DNA levels, change from Baseline in serum HBV DNA concentrations, serum ALT concentrations, and change from Baseline in serum ALT levels were to be presented by visit and treatment group. These endpoints were to be tested using an ANCOVA model with effects for Baseline stratification factors (HBeAg negative vs positive status, 12-24 vs 25-52 weeks of prior lamivudine therapy), geographic region, gender, age, race, Baseline HBV DNA, and Screening ALT at the 0.05 significance level.

The number and percentage of patients achieving each of the discrete endpoints were to be presented by treatment group for Week 24, Week 48, and Week 52. However, the following discrete secondary endpoints were summarized at all visits up to Week 52: serum HBV DNA suppression, HBV DNA undetectable, ALT normalized, ALT normalization, composite serologic response, HBeAg loss, HBeAg seroconversion. Also, maintained discrete secondary endpoints and Treatment Failure were only summarized at Week 52. Statistical testing for treatment group differences for the discrete secondary efficacy parameters by study week were to be based on the Cochran-Mantel-Haenszel (CMH) chi-squared test of general association stratified by Baseline stratification factors (HBeAg negative vs positive status, 12-24 vs 25-52 weeks of prior lamivudine therapy).

For continuous efficacy parameters, an Analysis of Variance (ANOVA) model with effects for Baseline stratification factors (HBeAg negative vs positive status, 12-24 vs 25-52 weeks of prior lamivudine therapy) was to be used. P-values for least-square means treatment differences by study week were to be presented. The null hypothesis to be tested was that the difference in proportions for each pairwise treatment comparison is 0.

Summary - Conclusions

Efficacy results:

Results at Week 24:

Primary efficacy results

At Week 24, patients in the telbivudine treatment group showed a statistically significantly larger reduction from Baseline in mean serum HBV DNA as compared to patients in the lamivudine group. At Week 24 the mean serum HBV DNA concentration for patients in the LdT group was significantly lower compared to those in the Lam treatment group (Table 2-1).

Table 2-1 Change from Baseline in Serum HBV DNA and Serum HBV DNA (log_{10} copies/mL) at Week 24

Parameter	Statistic	Lam N = 124	LdT N = 122	p-value
Change from Baseline in Serum HBV DNA	Mean (SE)	-0.899 (0.266)	-1.896 (0.184)	<0.001
Serum HBV DNA	Mean (SE)	5.068 (0.260)	3.780 (0.187)	<0.001

Source: Table 14.2.1.1

Note: Missing values are imputed up to Week 24 using LOCF from the last reported post-Baseline on-treatment visit.

Note: Percentages are based on the number of patients in each treatment group eligible for meeting the endpoint.

Note: For all secondary endpoints the SAP definitions were used. Please see Table 9-5 for differences between protocol and SAP definitions.

Note: P-values for all other continuous variables are from an ANCOVA model with covariates for randomization strata (HBeAg negative vs. positive status, 12-24 vs. 25-52 weeks of prior Lamivudine therapy), geographic region, gender, race (Asian, Other), age, Baseline serum HBV DNA, and Baseline ALT.

Secondary efficacy results

Serum HBV DNA was undetectable in a higher proportion of LdT treated patients than in Lam treated patients although this difference did not reach statistical significance. Serum HBV DNA suppression, loss of HBeAg, and HBeAg seroconversion occurred in a similar percentage of

patients in the LdT and Lam groups and no statistically significant differences between the treatment groups were observed for these variables. Loss of HBsAg and HBsAg seroconversion did not occur in any patients, in either treatment group. Therapeutic response was comparable between the two groups.

LdT treatment resulted in numerically superior results compared with lamivudine treatment for the majority of secondary endpoints however, statistical significance was not achieved (Table 2-2).

Table 2-2 Efficacy Results at Week 24 of Treatment

Parameter	Statistic	Lam N = 124	LdT N = 122	p-value
HBV DNA Undetectable	n/N (%)	39/124 (31)	49/121 (40)	0.097
HBV DNA Suppression	n/N (%)	8/53 (15)	8/47 (17)	0.770
HBeAg Loss	n/N (%)	7/81 (9)	8/81 (10)	0.569
HBeAg Seroconversion	n/N (%)	6/81 (7)	8/81 (10)	0.364
HBsAg Loss	n/N (%)	0/124	0/121	
HBsAg Seroconversion	n/N (%)	0/124	0/121	
ALT Normalization	n/N (%)	36/53 (68)	26/53 (49)	0.067
ALT Normalized	n/N (%)	47/65 (72)	40/67 (60)	0.143
ALT Concentration (IU/L)	Mean (SE)	50.6 (7.2)	44.1 (3.6)	0.408
Change from Baseline in ALT (IU/L)	Mean (SE)	-7.1 (7.6)	-24.7 (7.1)	0.408
Therapeutic Response	n/N (%)	27/104 (26)	27/103 (26)	0.989

Source: Table 14.2.1.1

Note: Missing values are imputed up to Week 24 using LOCF from the last reported post-Baseline on-treatment visit.

Note: P-values for discrete parameters are from a CMH Chi-square test of general association stratified by randomization strata (HBeAg negative vs. positive status, 12-24 vs. 25-52 weeks of prior lamivudine therapy).

Note: P-values for continuous variables (ALT and Change from Baseline in ALT) are from an ANCOVA model with covariates for randomization strata (HBeAg negative vs. positive status, 12-24 vs. 25-52 weeks of prior Lamivudine therapy), geographic region, gender, race (Asian, Other), age, Baseline serum HBV DNA, and Baseline ALT.

Results at Week 52:

Secondary efficacy results

At Week 52 mean serum HBV DNA levels in patients treated with LdT were significantly lower than in patients treated with Lam. Mean reductions in HBV DNA levels from Baseline were significantly greater in patients receiving LdT compared with patients receiving Lam. Serum HBV DNA at Week 52 was undetectable in significantly more patients who received LdT compared with those who received Lam. Similarly, a significantly higher proportion of patients in the LdT treatment group had maintained undetectable HBV DNA at Week 52 compared with those patients in the Lam treatment. Patients receiving LdT generally demonstrated a higher rate of HBV DNA suppression than patients receiving Lam for 52 weeks (Table 2-3).

For liver function parameters, there were no statistically significant differences between the treatment groups at Week 52 for mean ALT concentration or mean ALT changes from Baseline. The proportions of patients with ALT normalization, ALT normalized, and maintained ALT normalization were proportionally better in the LdT group compared with the Lam group at Week 52 (Table 2-3 and Table 14.2.1.2). Thus, for all of the ALT parameters measured, treatment with telbivudine demonstrated numerically better results than treatment with lamivudine, although statistical significance was not achieved.

The proportion of patients experiencing Treatment Failure was significantly greater for those treated with Lam compared with LdT treated patients. Primary Treatment Failure was statistically significantly higher in patients receiving Lam compared to patients who received LdT. Secondary Treatment Failure did not reach significance between the two treatment groups (Table 2-3).

The percentage of patients with Virologic Breakthrough at Week 48 and at Week 52 was significantly greater for those patients treated with Lam compared with those treated with LdT (Table 2-3).

Table 2-3 Efficacy Results at Week 52 of Treatment

Parameter	Statistic	Lam N = 124	LdT N = 122	p-value
Change from Baseline in Serum HBV DNA (log_{10} copies/mL)	Mean (SE)	-0.084 (0.307)	-1.476 (0.278)	<0.001
Serum HBV DNA (log_{10} copies/mL)	Mean (SE)	5.884 (0.296)	4.201 (0.247)	<0.001
HBV DNA Undetectable	n/N (%)	38/124 (31)	56/121 (46)	0.005
HBV DNA Suppression	n/N (%)	6/53 (11)	14/47 (30)	0.060
Maintained Undetectable HBV DNA	n/N (%)	33/118 (28)	54/119 (45)	0.002
HBeAg Loss	n/N (%)	11/81 (14)	15/81 (19)	0.277
Maintained HBeAg Seroconversion	n/N (%)	8/81 (10)	12/81 (15)	0.212
ALT Normalized	n/N (%)	37/65 (57)	44/67 (66)	0.239
ALT Normalization	n/N (%)	27/53 (51)	32/53 (60)	0.202
Maintained ALT Normalization	n/N (%)	26/53 (49)	29/53 (55)	0.359
ALT Concentration (IU/L)	Mean (SE)	49.4 (5.4)	43.9 (4.9)	0.498
Change from Baseline in ALT (IU/L)	Mean (SE)	-8.4 (6.7)	-24.9 (8.1)	0.498
1-log above nadir Virologic Breakthrough (Week 48)	n/N (%)	51/124 (41)	28/121 (23)	0.002
1-log above nadir Virologic Breakthrough (Week 52)	n/N (%)	57/124 (46)	34/121 (28)	0.002
Treatment Failure	n/N (%)	29/122 (24)	8/121 (7)	<0.001
Primary Treatment Failure	n/N (%)	25/122 (20)	6/121 (5)	<0.001
Secondary Treatment Failure	n/N (%)	4/122 (3)	2/121 (2)	0.398

Source: Table 14.2.1.2

Note: Percentages are based on the number of patients in each treatment group eligible for meeting the endpoint.

Note: For all secondary endpoints the SAP definitions were used. Please see Table 9-5 for differences between protocol and SAP definitions.

Note: P-values for discrete parameters are from a CMH Chi-square test of general association stratified by randomization strata (HBeAg negative vs. positive status, 12-24 vs. 25-52 weeks of prior Lamivudine therapy). Note: P-value for change from Baseline in serum HBV DNA concentration is from an ANCOVA model with covariates for randomization strata (HBeAg negative vs. positive status, 12-24 vs. 25-52 weeks of prior Lamivudine therapy), Baseline serum HBV DNA, and age.

Note: P-values for all other continuous variables are from an ANCOVA model with covariates for randomization strata (HBeAg negative vs. positive status, 12-24 vs. 25-52 weeks of prior Lamivudine therapy), geographic region, gender, race (Asian, Other), age, Baseline serum HBV DNA, and Baseline ALT.

Strata analyses

The population of patients was stratified by HBeAg status and length of prior lamivudine treatment. Patients were either HBeAg positive or negative and had previously received three to 12 months of treatment with lamivudine. Strata were treated as covariates and their effects were controlled for in the analyses, however, the study was not powered to detect any differences in the primary efficacy endpoint between strata. These are exploratory analyses which are useful as descriptive evaluations of HBeAg status and length of prior lamivudine treatment. The Week 52 analyses of the randomization strata used inferential statistical tests whereas the Week 24 analyses of these strata used descriptive statistics.

At Week 52 those HBeAg positive patients previously treated with 12-24 weeks or 25-52 weeks of lamivudine therapy and receiving LdT during the current study had statistically superior results for several endpoints such as serum HBV DNA levels, change from Baseline in serum HBV DNA, HBV DNA undetectable, maintained undetectable HBV DNA, viral breakthrough, Treatment Failure, and Primary Treatment Failure, in comparison to those patients receiving lamivudine in the current study. Due to the small number of patients in the HBeAg negative strata, no definitive conclusions about the key efficacy parameters could be made.

Treatment emergent HBV viral genotypes

This will be provided in a separate document.

Safety results: The study drugs were generally safe and well tolerated. The clinical adverse event profile of telbivudine appears similar to that of lamivudine. There was one death in the study which occurred in a patient receiving lamivudine and which was not considered by the investigator to be reasonably or possibly related to the study drug. During screening, one patient had an SAE of acute tonsillitis which resulted in death. Three patients had treatment prematurely discontinued during the study.

On-treatment AEs were reported in 51% of patients and were similarly distributed across treatment groups. Not more than 15% of patients experienced an AE which was considered to be related to study drug at any point during the study. Three AEs led to discontinuation from study medication. Two patients treated with Lam and one treated with LdT experienced one AE each leading to discontinuation of study medication. One patient in the Lam treatment group experienced an AE of hepatic enzyme increased which was considered reasonably or possibly related to study drug. The other two AEs of cardiac arrest (Lam group) and hepatic enzyme increased (LdT group) were considered not reasonably or possibly related to study medication.

A total of 13 patients (5%) (Lam, n=8 and LdT, n=5) reported on-treatment SAEs during the study however, no patients experienced SAEs that were considered by the Investigator to be related to study drug. Each SAE reported was experienced by only one patient except for the SAE of myocardial infarction and haemorrhoids which were each experienced by two patients.

Overall, 71% of patients experienced a post-Baseline, on-treatment, Grade 1 or 2 laboratory abnormality. The number of patients in each treatment group experiencing a Grade 1 or 2 laboratory abnormality was similar across treatment groups. Nine percent of patients (n=21) experienced a post-Baseline, on-treatment, Grade 3 or 4 laboratory abnormality.

There were a total of four patients with investigator-described myalgia (Lam, n=1 and LdT, n=3). Three of the four patients experienced a Grade 1 AE of myalgia (Lam, n=1 and LdT, n=2) which in most cases did not require treatment. In only one case did the investigator consider the event to be reasonably or possibly related to the study drug (Lam, n=1).

The number of patients in each treatment group meeting at least one on-treatment criterion for AASLD-defined ALT flare was similar between the groups (Lam, 3% and LdT, 2%). Investigator reported adverse events of ALT elevation in either treatment group were generally categorized as Grade 1 or 2 toxicities and considered not reasonably or possibly related to the study drug.

Bioanalytical results: No pharmacokinetic analyses were performed during the study.

Conclusion:

- Telbivudine demonstrated significantly greater antiviral efficacy than lamivudine at Week 24 as demonstrated in the reduction from Baseline in HBV DNA level, the primary efficacy endpoint.
- Patients treated with telbivudine showed lower mean serum HBV DNA concentrations and a greater change from Baseline in serum HBV DNA at Week 52.
- The study was not powered to detect differences between secondary endpoints, with the exception of maintained ALT normalization, which was not met.
- As a result of the protocol not requiring testing of the YMDD-mutant at Baseline it was not possible to rule out lamivudine resistance or a pre-existing mutation. The overall results may be confounded by this. It is not possible to conclude that telbivudine is the more potent agent or if more lamivudine patients developed resistance.
- All treatments were generally safe and well tolerated.
- There was one on-treatment death in the Lam treatment group which was considered by the investigator to be not related to the study medication.
- Clinical adverse events and laboratory toxicity grades were similar between treatment groups.

Date of the report: 05-October-2007