2. SYNOPSIS

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Title of study	:	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of FDC tablet GPO-VIR® S30 containing Stavudine 30 mg +Lamivudine 150 mg+Nevirapine 200 mg of The Government Pharmaceutical Organization, Thailand and Zerit* (Stavudine) 30 mg capsules of Bristol- Myers Squibb, Pharmaceuticals USA + Epivir ™ (Lamivudine) 150 mg tablets of GlaxoSmithKline, Pharmaceuticals Ltd., UK + Viramune® (Nevirapine) 200 mg tablets of Boehringer Ingelheim Pharmaceuticals Inc., Germany, in healthy human adult male subjects, under fasting conditions.
Investigators	:	Principal Investigator: Dr. James John, MBBS, MD Lotus Labs. Pvt. Ltd., Bangalore Clinical Investigator: Dr. Chethana N. Vishwanath, BSc, MBBS Lotus Labs. Pvt. Ltd., Bangalore Co- Investigator: Dr. Nanda Kumari P MBBS Lotus Labs. Pvt. Ltd., Bangalore Co- Investigator: Dr. Kenuite F M MBBS Lotus Labs. Pvt. Ltd., Bangalore
Study centre	:	Lotus Labs Pvt. Ltd., St. John's National Academy of Health Sciences, 141/2, John Nagar, Koramangala III Block, Bangalore - 560 034
Study start date	:	06 April 2007
Study completion date	:	21 May 2007
Objective	:	To assess the bioequivalence of FDC tablet GPO-VIR® S30 containing Stavudine 30 mg+Lamivudine 150 mg+Nevirapine

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

		200 mg of The Government Pharmaceutical Organization, Thailand and Zerit* (Stavudine) 30 mg capsules of Bristol-Myers Squibb, Pharmaceuticals, USA + Epivir™ (Lamivudine) 150 mg tablets of GlaxoSmithKline, Pharmaceuticals Ltd., UK + Viramune® (Nevirapine) 200 mg tablets of Boehringer Ingelheim Pharmaceuticals Inc., Germany, in healthy human adult male subjects, under fasting conditions.
Methodology	:	A total of 36 healthy adult male subjects were enrolled for the study and housed for at least 61 hours (at least 13 hours prior to drug administration to 48 hours post dose blood draw). The subjects were dosed either with the test or reference product in each period as determined by the randomization schedule. The blood samples were collected within one hour before dosing and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, 72.00, 120.00, 168.00, 216.00 and 264.00 hours post-dosing in both periods. There was a washout period of 28 days between the dosings.
Number of subjects	:	• No. of subjects planned: 36 • No. of subjects dosed in period I: 36 • No. of subjects dosed in period II: 30 • No. of subjects withdrawn: 04 • No. of subjects dropped out: 02 • No. of subjects completed: 30 • No. of subjects analyzed: 30 • No. of subjects included in pharmacokinetic and statistical analysis: 30 • No. of subjects analysed in the bioanalytical laboratory for safety reasons: Nil

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Main criteria for inclusion:		Healthy, human male adult subjects aged between 18-50 years (inclusive) weighing as per the standard height and weight chart of Life Insurance Corporation of India (II Underweight and Overweight Min. & Max. Chart) who had no evidence of underlying disease or significant abnormal laboratory values at screening and who voluntarily consented to participate in the study.
Test product A	:	GPO-VIR® S30
Lot no	:	S490256
Manufacturing date	:	03 October 2006
Expiry date	:	03 October 2008
Dose and mode of administration	:	Single oral dose administered with 240 ml of water under fasting conditions
Reference product B: (Reference product I)		ZERIT* (Stavudine) 30 mg capsules
Lot no	:	6E14037A
Manufacturing date	:	21 July 2006
Expiry date	:	31 July 2008
Reference product B : (Reference product II)		Epivir™ (Lamivudine) 150 mg tablets
Batch no	:	MZ0021
Manufacturing date	:	19 May 2006
Expiry date	:	18 May 2011

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Reference product B : (Reference product III)		Viramune® (Nevirapine) 200 mg tablets
Batch no	:	604342
Manufacturing date	:	April 2006
Expiry date	:	April 2009
Mode of administration :		Single oral dose of reference products B [reference product I (ZERIT® (Stavudine) 30 mg capsules), reference product II (Epivir™ (Lamivudine) 150 mg tablets) and reference product III (Viramune® (Nevirapine) 200 mg tablets)] administered with 240 ml of water under fasting conditions.
Duration of treatment	:	A single oral dose of the test or reference product was administered on two different occasions separated by a washout period of 28 days.
Analytical methods	:	• Method: LC-MS/MS, Solid phase extraction Method • Analyte: Stavudine, Lamivudine and Nevirapine • Calibration Curve Range: • 0.0206 µg/ml to 2.4524 µg/ml for Stavudine • 0.0206 µg/ml to 2.9553 µg/ml for Lamivudine • 0.0261 µg/ml to 4.9452 µg/ml for Nevirapine

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Pharmacokinetic analysis:	• Primary Pharmacokinetic parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. • Secondary Pharmacokinetic parameters: T_{max}, K_{el}, $t_{1/2}$ and $AUC_{0-t}/AUC_{0-\infty}$ • Software: Pharmacokinetic analysis was by Non-compartmental method of analysis using the WinNonlin® Professional Version 5.0.1 • As per protocol, Stavudine plasma concentration up to 12.0 hrs of sampling and Lamivudine plasma concentration up to 36.0 hrs of sampling were considered to provide complete profiling of the drug • Number of subjects included for pharmacokinetic analysis: 30
Statistical methods :	• Software: SAS® package (Version 9.1) • Arithmetic mean, standard deviations, minimum, maximum, median and percentage coefficient of variation were calculated for the pharmacokinetic parameters. • Additionally geometric means were calculated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ • The log transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were analysed using a GLM ANOVA model • 90% confidence intervals for the difference between drug formulation least-square means were calculated for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using log - transformed data.
Criteria for evaluation :	The following standards for bioequivalence were applied: The 90% confidence interval of the relative mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test and reference product of Stavudine, Lamivudine and Nevirapine should be between 80.00% and 125.00% for log - transformed data.

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Safety results	:	There were ten adverse events reported during the study of which four were related and six unrelated to the study products. All the four related AEs were caused by the reference product. All adverse events were mild to moderate in intensity and resolved completely without any sequelae except one AE (Tinea versicolor) for subject No. 01 is ongoing. As the adverse event is considered to be unrelated to the study products and the subject was clinically asymptomatic no further follow up was required. One medical event (vasovagal syncope) was reported in subject No.26 which resolved completely without intervention and the subject was dosed. There were no serious adverse events in the study. In this study both the test and reference products were considered to be safe and well tolerated.

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Table 1

Summary of Pharmacokinetic data for Stavudine

Dose =30 mg
Zerit® (Stavudine) (Reference product)

Pharmacokinetic Parameter	Geometric Mean	Arithmetic Mean	Standard Deviation
C_{max} (µg/ml)	0.5141	0.5253	0.1144
AUC_{0-t} (µg.h/ml)	1.4698	1.4968	0.2962
$AUC_{0-\infty}$ (µg.h/ml)	1.5798	1.6089	0.3173

GPO-VIR® S30 (Test product)

Pharmacokinetic Parameter	Geometric Mean	Arithmetic Mean	Standard Deviation
C_{max} (µg/ml)	0.5297	0.5539	0.1725
AUC_{0-t} (µg.h/ml)	1.5253	1.5493	0.2962
$AUC_{0-\infty}$ (µg.h/ml)	1.6447	1.6701	0.2860

Table 2
Ratio and 90% Confidence Intervals of Test versus Reference for Stavudine

Pharmacokinetic Parameter	Ratio (%)	90% Confidence Intervals (%)
C_{max} (µg/ml)	103.03	94.60 to 112.21
AUC_{0-t} (µg.h/ml)	103.43	99.96 to 107.02
$AUC_{0-\infty}$ (µg.h/ml)	103.76	100.16 to 107.49

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Table 3

Summary of Pharmacokinetic data for Lamivudine

Dose =150 mg

Epivir™ (Lamivudine) (Reference product)

Pharmacokinetic Parameter	Geometric Mean	Arithmetic Mean	Standard Deviation
C_{max} (µg/ml)	1.0315	1.0998	0.3849
AUC_{0-t} (µg.h/ml)	5.7578	6.1110	2.0237
$AUC_{0-\infty}$ (µg.hr/ml)	5.9439	6.2888	2.0341

GPO-VIR® S30 (Test product)

Pharmacokinetic Parameter	Geometric Mean	Arithmetic Mean	Standard Deviation
C_{max} (µg/ml)	1.1657	1.2148	0.3370
AUC_{0-t} (µg.h/ml)	6.3730	6.6137	1.7536
$AUC_{0-\infty}$ (µg.h/ml)	6.5664	6.7984	1.7521

Table 4

Ratio and 90% Confidence Intervals of Test versus Reference for Lamivudine

Pharmacokinetic Parameter	Ratio (%)	90% Confidence Intervals (%)
C_{max} (µg/ml)	112.95	100.59 to 126.82
AUC_{0-t} (µg.h/ml)	110.43	102.32 to 119.18
$AUC_{0-\infty}$ (µg.h/ml)	110.23	102.40 to 118.65

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Table 5

Summary of Pharmacokinetic data for Nevirapine

Dose =200 mg

Viramune® (Nevirapine) (Reference product)

Pharmacokinetic Parameter	Geometric Mean	Arithmetic Mean	Standard Deviation
C_{max} (µg/ml)	2.5624	2.6013	0.4398
AUC_{0-t} (µg.h/ml)	191.5513	194.7174	38.0705
$AUC_{0-\infty}$ (µg.h/ml)	205.2682	209.2910	44.3698

GPO-VIR® S30 (Test product)

Pharmacokinetic Parameter	Geometric Mean	Arithmetic Mean	Standard Deviation
C_{max} (µg/ml)	2.3379	2.3787	0.4627
AUC_{0-t} (µg.h/ml)	188.6065	192.1413	37.3245
$AUC_{0-\infty}$ (µg.h/ml)	200.0402	204.5378	43.7477

Table 6

Ratio and 90% Confidence Intervals of Test versus Reference for Nevirapine

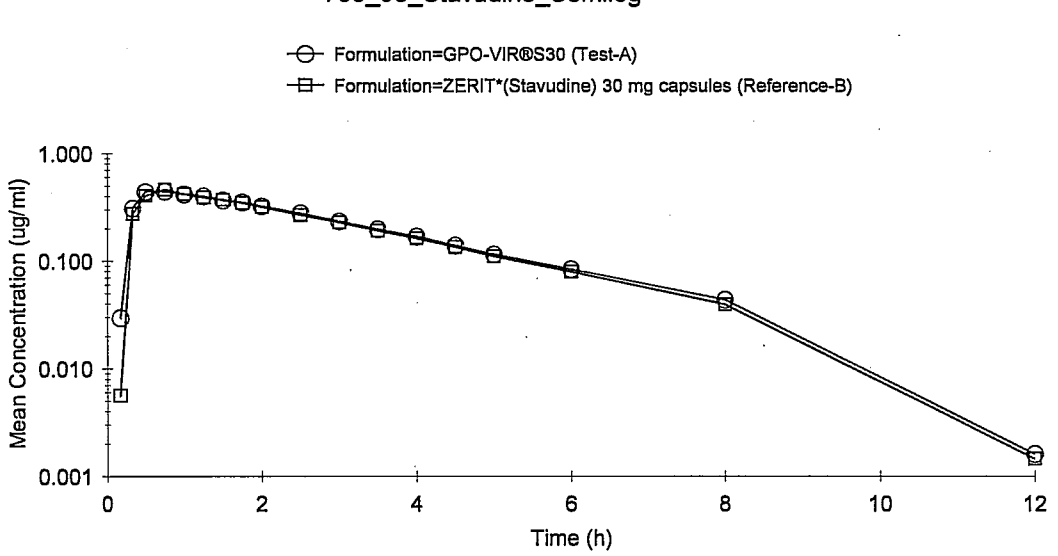
Pharmacokinetic Parameter	Ratio (%)	90% Confidence Intervals (%)
C_{max} (µg/ml)	91.10	86.85 to 95.55
AUC_{0-t} (µg.h/ml)	98.41	95.52 to101.40
$AUC_{0-\infty}$ (µg.h/ml)	97.49	94.91 to 100.14

NAME OF SPONSOR: The Government Pharmaceutical Organization, Thailand	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: GPO-VIR® S30	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Stavudine + Lamivudine + Nevirapine		

Summary conclusion :	Based on the results obtained in the study The 90% confidence interval of the relative mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test and reference product of Stavudine and Nevirapine were between 80.00% and 125.00% for log - transformed data. The 90% confidence interval of the relative mean AUC_{0-t} and $AUC_{0-\infty}$ of the test and reference product of Lamivudine were between 80.00% and 125.00% for log - transformed data except for C_{max} whose 90% confidence interval was between 100.59% to 126.82%. Based on the results obtained in the study FDC tablet GPO-VIR® S30 containing Stavudine 30 mg+Lamivudine 150 mg + Nevirapine 200 mg of The Government Pharmaceutical Organization, Thailand and Zerit* (Stavudine) 30 mg capsules of Bristol- Myers Squibb, Pharmaceuticals, USA+Epivir™ (Lamivudine) 150 mg tablets of GlaxoSmithKline, Pharmaceuticals Ltd., UK+Viramune® (Nevirapine) 200 mg tablets of Boehringer Ingelheim Pharmaceuticals Inc., Germany, were not bioequivalent in healthy human adult male subjects, under fasting conditions. In this study both the test and reference products were considered to be safe and well tolerated.
Date of the Report :	03 October 2007

Figure 1

Semi-log and Linear Plot of Mean Plasma Stavudine Concentrations versus Time Profiles in Healthy Human Adult Male Subjects



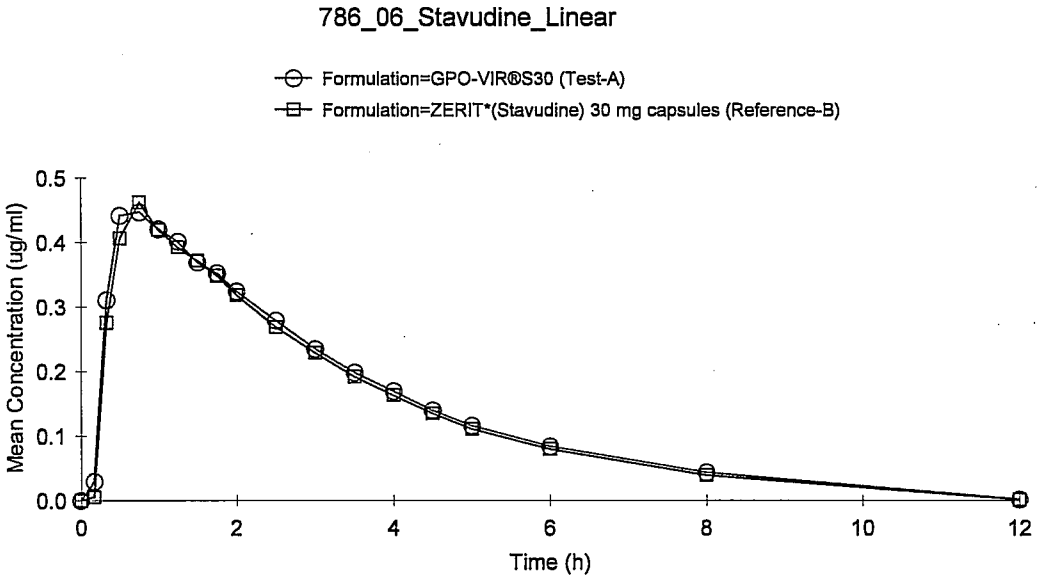
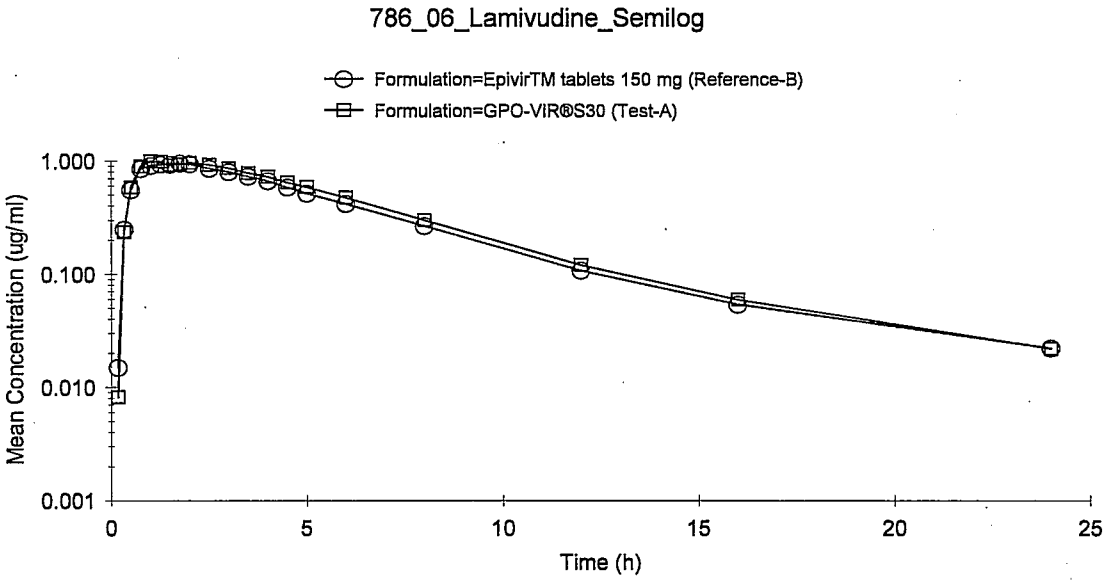


Figure 2

Semi-log and Linear Plot of Mean Plasma Lamivudine Concentrations versus Time Profiles in Healthy Human Adult Male Subjects



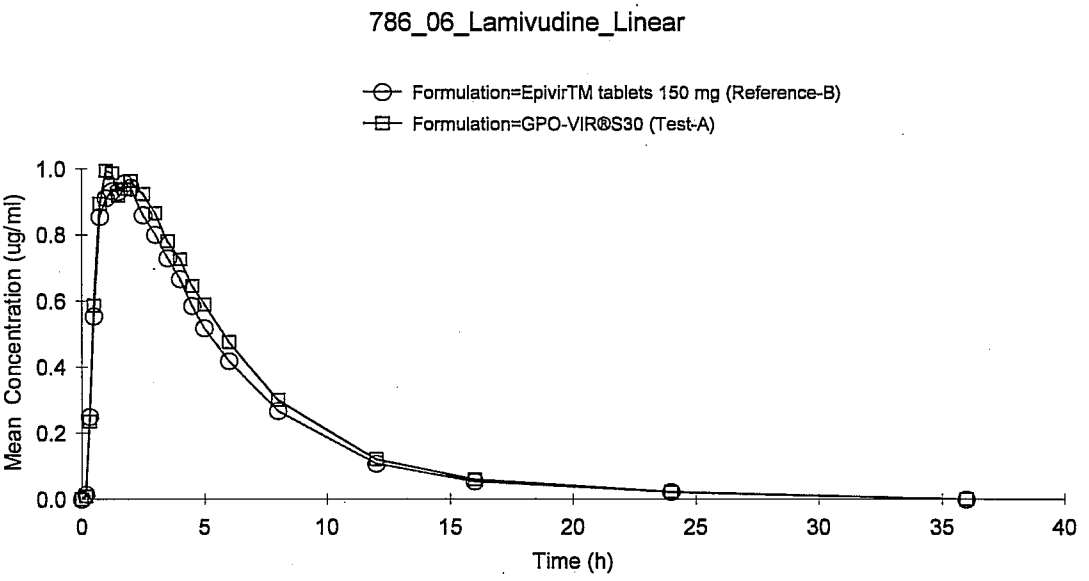


Figure 3

Semi-log and Linear Plot of Mean Plasma Nevirapine Concentrations versus Time Profiles in Healthy Human Adult Male Subjects