2. STUDY SYNOPSIS

Generic Name:	Tenofovir disoproxil furamate 300 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Tenofovir GPO® 300 mg tablets	
Reference Product:	Viread™ 300 mg tablets	
Study Title:		Comparative Randomized, Single Dose, Two-Way Crossover, Open-Label Pivotal Study to Determine the Bioequivalence of Tenofovir Disoproxil Furamate Formulations, Tenofovir GPO® 300 mg Tablets and Viread™ 300 mg Tablets, After Oral Administration to Healthy Thai Male Volunteers Under Fasting Conditions
Investigators:		Study Director: Dr.Isariya Techatanawat Principal Investigator: Ms.Piengthong Narakorn Clinical Investigator: Dr.Archawin Rojanawiwat Analytical Investigator: Dr. Bancha Chuasuwan PK & Statistic Investigator: Ms.Piengthong Narakorn
Protocol Number:		022-12
Project Number:		BE002-13
Ethics Committee Approval Date:		Institute for the Development of Human Research Protections (IHRP) Approval date 16 Oct 2012, 23 Apr 2013(1st amendment)
Objectives:		To compare the rate and extent of absorption of tenofovir from tenofovir disoproxil furamate 300 m g tablets formulation and with that of reference formulation. To evaluate the safety and tolerability of the formulations in healthy subjects on t he basis of clinical and laboratory examinations at the beginning and at the end of the trial.

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir disoproxil furamate 300 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Tenofovir GPO® 300 mg tablets	
Reference Product:	Viread™ 300 mg tablets	
Dosage Regimen:		Test Product: Single dose, 300 mg of Tenofovir GPO® tablets. Batch No. A550931 Mfg. Date 26 Apr 2012 Exp. Date 26 Apr 2014 Manufactured by: The Government Pharmaceutical Organization, Bangkok, Thailand Reference Product: Single dose, 300 mg of Viread™ tablets. Batch No. W178485D Mfg. Date Jan 2012 Exp. Date Jan 2015 Manufactured for: Gilead Science, Inc. Foster, USA Manufactured by: Nycomed GmbH, Oranienburg, Germany Name and address of importer or authorization holder: IDS Marketing (Thailand) Ltd. Ayuthdhaya, Thailand/ LF Asia. Thailand
Clinical Study Site:		Clinical Research Center, Department of Medical Sciences, Ministry of Public Health, Thiwanon Rd., Amphur Mueng, Nontaburi, Thailand 11000
Study Subjects:		40 subjects, selected randomly from healthy adult Thai male volunteers. No. of subjects enrolled: 40 No. of subjects withdrawn: 4 No. of subjects completed: 36 No. of subjects analyzed: 40 No. of subjects included in pharmacokinetics and statistical analysis: 36

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir disoproxil furamate 300 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Tenofovir GPO® 300 mg tablets	
Reference Product:	Viread™ 300 mg tablets	
Demographic Data of Enrolled Subjects (N=40):		Age = 29.00±8.43 years; Height = 171.38±6.50 cm; Weight= 64.76±6.63 kg, BMI= 22.04±1.68 kg/m^2
Demographic Data of Completed Subjects (N=36):		Age = 29.19± 8.81 year, Height = 170.86 ± 6.63 cm, Weight = 64.46 ± 6.55 kg, BMI= 22.08 ± 1.65 kg/m^2
Admission and Confinement:		Subjects were admitted the night before study drug administration, supervised for at least 10.0 hours prior to drug administration until after the 48.0 hours post dose blood samples were drawn and followed up for ambulatory blood collection at 72.0 hours.
Drug Administration:		Each subject randomly received a single dose of the assigned formulation, administered with 240 ml of water after an overnight fasting of at least 10.0 hrs.
Study Period:		Screening: 24–26 and 29 Apr 2013 Enrollment: 6 – 18 May 2013 Period I: 6 – 10 May 2013 Period II: 14 – 18 May 2013
Washout Period:		8 days
Blood Sampling Schedule:		20 blood samples (05 mL for post dose and 07 mL for pre-dose sample) were drawn at 0.000 (pre-dose sample) and 0.167, 0.333, 0.500, 0.667, 0.833, 1.000, 1.250, 1.500, 2.000, 3.000, 4.000, 6.000, 8.000, 12.000, 16.000, 24.000, 36.000, 48.000 and 72.000 hours (post-dose). The total volume of blood drawn did not exceed 224 ± 10 mL.

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir 300 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Tenofovir GPO® 300 mg tablets	
Reference Product:	Viread™ 300 mg tablets	
Blood Sampling Handling:		The blood samples were allowed to coagulate for at least 45 minutes and then the blood samples were placed in a refrigerated centrifuge within 60 minutes from the time of collection and centrifuged. The blood samples were centrifuged at 3000 ± 100 g for 5 minutes below 10°C to separate serum. The blood samples were kept in wet ice bath before centrifugation and during separation. The separated serum were transferred to pre labeled polypropylene tubes in two aliquots [around 1.7 mL in the first lot (around 2.2 m L in case of pre-dose sample) and rest of the volume in the second lot] and stored upright in a box containing dry ice or in a freezer at a temperature -65 ± 10°C for interim storage until shipment to analytical facility for analysis. Shipments were done separately for each set of aliquots.
Clinical Sample Storage:		Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization
Analytical Site:		Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization
Bioanalytical Methodology:		Serum samples of subjects were assayed for Tenofovir using a validated LC-MS/MS method.
Analyte:		Tenofovir in human serum
Safety Evaluation:		Both treatments were well tolerated for all study subjects. No clinically significant or serious ADR were observed.
Surrogate Parameters:		Drug plasma concentrations to indicate therapeutic effect.

Generic Name:	Tenofovir 300 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Tenofovir GPO® 300 mg tablets	
Reference Product:	Viread™ 300 mg tablets	

Primary Pharmacokinetic Parameters:

The primary pharmacokinetic parameters employed for tenofovir were $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}.

The mean ± SD values of primary pharmacokinetic parameters of tenofovir for Test Product-T and Reference Product-R for thirty-six subjects were summarized in the following table :

Parameters (Units)	(Un-transformed data)	
	Test-T	Reference -R
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	2947.612 ± 659.0106	2857.115 ± 755.5534
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	3198.758 ± 745.4046	3072.687 ± 769.6531
C_{max} (ng/mL)	401.057 ± 160.5996	377.662 ± 107.6902

Secondary Pharmacokinetic Parameters:

The secondary pharmacokinetic parameters employed for tenofovir were Tmax , λz , t1/2, AUC0-tlast/ AUC0-∞ and AUC_%Extrap_obs.

Parameters (Units)	(Un-transformed data)	
	Test-T	Reference -R
T_{max} (hr)*	0.750 (0.350,4.000)	0.667 (0.333,2.000)
λ_z (1 / hr)	0.040 ± .0063	0.040 ± 0.0071
$t_{½}$ (hr)	17.956 ± 3.0994	18.192 ± 4.1732
$AUC_{0\text{-tlast}}$ / $AUC_{0\text{-}\infty}$	0.923 ± 0.0455	0.927 ± 0.0271
AUC_%Extrap_obs (%)	7.720 ± 4.5528	7.260 ± 2.7058

*Tmax were represented in median (Min, Max) value.

<table>
<tr><td>Generic Name:</td><td>Tenofovir 300 mg tablets</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product:</td><td>Tenofovir GPO® 300 mg tablets</td></tr>
<tr><td>Reference Product:</td><td>Viread™ 300 mg tablets</td></tr>
<tr><td colspan="2">90% Confidence Intervals:</td><td>The 90% confidence intervals were calculated for the ln-transformed primary pharmacokinetic parameters, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} of tenofovir and presented as below.
<table>
<tr><th>Parameters</th><th>Ratios</th><th>90% CI</th></tr>
<tr><td>ln $AUC_{0\text{-tlast}}$</td><td>103.8</td><td>99.02-108.83</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>104.4</td><td>99.38-109.72</td></tr>
<tr><td>ln C_{max}</td><td>102.8</td><td>95.59-110.65</td></tr>
</table></td></tr>
<tr><td colspan="2">Conclusion:</td><td>The Test Product-T (Tenofovir GPO 300 m g tablets – Manufactured by: GPO, Thailand. / Batch Number – A550931) when compared with the Reference Product-R (Viread™ 300 mg tablets – Manufactured by: Nycomed GmbH, Germany / Batch No. W178485D) met the bioequivalence criteria of 80.0-125.0% with respect to the rate and extent of absorption.</td></tr>
<tr><td colspan="2">Date of Report:</td><td>22 Aug 2013</td></tr>
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