## 2. STUDY SYNOPSIS

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|---|---|
| **Generic Name:** Tenofovir | **Sponsor's Name:** The Government Pharmaceutical Organization |
| **Test Product:** Tenevir 300 mg Tablets | |
| **Reference Product:** Viread™ 300 mg Tablets | |
| **Study Title:** | Comparative Randomized, Single Dose, Two-Way Crossover, Open-Label Study to Determine the Bioequivalence of Tenofovir Disoproxil Fumarate Formulations, Tenevir 300 mg Tablets and Viread™ 300 mg Tablets, After Oral Administration to Healthy Thai Male Volunteers Under Fasting Conditions |
| **Investigators:** | **Study Director**<br>Dr. Isariya Techatanawat, B.Sc., Ph.D. |
| | **Principal Investigator:**<br>Professor Dr. Punnee Pitisuttithum, M.D., MBBS, D.T.M.&H, FRCPT |
| | **Clinical Investigator:**<br>Asst.Prof. Jittima Dhitavat, M.D.<br>Assoc.Prof. Varunee Desakorn<br>Dr. Viravarn Luvira, M.D. |
| | **Analytical Investigator:**<br>Dr. Bancha Chuasuwan, B.Sc., Ph.D.(Pharm) |
| | **Pharmacokinetic and Statistical Investigator**:<br>Ms. Busarat Karachot, M.Sc. (Pharmacology) |
| **Project Number:** | BE009-14 |
| **Protocol Number:** | P002-14 |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir<br>**Test Product:** Tenevir 300 mg Tablets<br>**Reference Product:** Viread™ 300 mg Tablets | **Sponsor's Name:**<br>The Government Pharmaceutical Organization |
| **IEC/IRB Approval Date:** | Ethics Committee of the Faculty of Tropical Medicine, Mahidol University<br>420/6 Ratchawithi Rd. Ratchathewi, Bangkok, Thailand 10400<br>Phone no. +66 2 3549100-19 # 1535, 1349<br>Fax no. + 66 2 3069126<br>Approval Date: 05 Aug 2014<br>(for period from 04 Aug 2014 to 03 Aug 2015)<br>Protocol version 02, dated 14 Mar 2014 |
| **Objectives:** | To compare the rate and extent of absorption of tenofovir from tenofovir disoprosil fumarate formulation with that of reference formulation.<br>To evaluate the safety of the formulations on the basis of clinical and laboratory examinations at the beginning and at the end of the trial. |
| **Dosage Regimen:** | **Test Product (T):**<br>Tenevir (tenofovir disoproxil fumarate) 300 mg Tablets<br>Each film coated tablet contains 300 mg of tenofovir disoproxil fumarate<br>Manufactured by: The Government Pharmaceutical Organization, Bangkok, Thailand. |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir<br>**Test Product:** Tenevir 300 mg Tablets<br>**Reference Product:** Viread™ 300 mg Tablets | **Sponsor's Name:**<br>The Government Pharmaceutical Organization |
| **Dosage Regimen (continued):** | Batch No. S550622<br>Mfg. Date 11 Dec 2012 Exp. Date 11 Dec 2014<br>**Reference Product (R):**<br>Viread™ (tenofovir disoproxil fumarate) 300 mg Tablets<br>Each film coated tablet contains 300 mg of tenofovir disoproxil fumarate<br>Manufactured by: Nycomed GmbH Oranienburg Germany<br>Manufactured for Gilead Science, Inc. Foster City, California, USA.<br>Imported by: IDS Marketing (Thailand) Ltd. Ayutthaya, Thailand.<br>Batch No. W178485D<br>Mfg. Date Jan 2012 Exp. Date Jan 2015 |
| **Clinical Study Site:** | Bioequivalence unit, Faculty of Tropical Medicine, Mahidol University<br>420/6 Ratchawithi road, Ratchathewi, Bangkok,Thailand 10400 |
| **Study Subjects:** | 40 subjects, selected randomly from healthy adult Thai male volunteers.<br>No. of subjects enrolled: 40<br>No. of subjects withdrawn/ dropped out: 1 (Subject No 1027 missed visit at 72.000 hours) |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir<br>**Test Product:** Tenevir 300 mg Tablets<br>**Reference Product:** Viread™ 300 mg Tablets | **Sponsor's Name:**<br>The Government Pharmaceutical Organization |
| **Study Subjects (continued):** | No. of subjects completed: 39<br>No. of subjects analyzed: 40<br>No. of subjects included in pharmacokinetics 40<br>No. of subjects included in statistical analysis: 39 |
| **Demographic Data (N=40):** | Age 26.7±6.0 year ; Height 169.9± 5.3 cm;<br>Weight 63.4±6.1 kg ; BMI 22.0±1.9 kg/$m^2$ |
| **Admission and Confinement:** | Subjects were housed in the clinical facility for three nights and five days in each period (Total two periods housing of the study will be six nights and ten days).The subjects stayed for one night or at least 10 hours in facility prior to IMP administration until 48 hours after dosing in each period. |
| **Drug Administration:** | After an overnight fast of at least 10 hours, one tablet of tenofovir disoproxil fumarate 300 mg of test or reference product was administered orally while in a sitting position, to each subject with 240 mL of drinking water, at ambient temperature by the study personnel. |
| **Study Period:** | Screening: 25 Aug 2014 – 02 Sep 2014<br>Period I: 07 Sep 2014 – 11 Sep 2014<br>Period II: 15 Sep 2014 – 19 Sep 2014 |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir | **Sponsor's Name:** The Government Pharmaceutical Organization |
| **Test Product:** Tenevir 300 mg Tablets | |
| **Reference Product:** Viread™ 300 mg Tablets | |
| **Washout Period:** | 08 days between period I and period II |
| **Blood Sampling Schedule:** | A total of 20 blood samples, each of around 05 mL (around 07 mL in case of pre dose sample) were collected from each subject in each period.<br><br>The venous blood samples were withdrawn at pre-dose (0.000) 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 following drug administration.<br><br>The pre-dose blood sample was collected within a period of 60 minutes before the dosing. Post-dose samples were collected at an interval of ± 02 minutes from the schedule time for all samples. Actual time of sample collection was recorded appropriately.<br>For each subject, combining the two periods, the total volume of blood drawn would be 260±10 mL. |
| **Blood Sampling Handling:** | Blood samples were allowed to coagulate for around 60 minutes and then the blood samples were placed in a refrigerated centrifuge and centrifuged. The blood samples were centrifuged at 3000 ± 100 rcf for 10 minutes below 10°C to separate serum. |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir | **Sponsor's Name:** The Government Pharmaceutical Organization |
| **Test Product:** Tenevir 300 mg Tablets | |
| **Reference Product:** Viread™ 300 mg Tablets | |
| **Blood Sampling Handling (continued):** | The blood samples were kept in wet ice water bath before centrifugation and during separation. The separated serum was transferred to prelabeled polypropylene tubes in two aliquots [around 0.5 mL in first lot (around 0.8 mL in case of pre-dose sample) and rest of the volume in second lot] and stored upright in a box containing dry ice or in a freezer at a temperature -55°C or colder for interim storage until shipment to analytical facility for analysis. Samples must be placed in the freezer or in dry ice box within 60 minutes from the start of centrifugation. Shipment was done separately for each set of aliquots.<br>During shipment the samples were packed in boxes containing adequate amount of dry ice. Temperature was recorded using calibrated temperature recording device during shipment at -55 $^{o}$C or colder.<br>A designated person from bioanalytical facility would receive the samples on arrival. The condition of the samples was examined on arrival. After receiving the samples at analytical facility, the samples were stored at –65 ± 10°C for final storage until completion of analysis. |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir<br>**Test Product:** Tenevir 300 mg Tablets<br>**Reference Product:** Viread™ 300 mg Tablets | **Sponsor's Name:**<br>The Government Pharmaceutical Organization |
| **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:** | Serum tenofovir concentration |
| **Safety Evaluation:** | Both treatments were well tolerated. No clinically significant or serious ADR were observed |
| **Surrogate Parameters:** | Drug serum concentrations to indicate clinical activity. |
| **Primary Pharmacokinetic Parameters:** | The primary pharmacokinetic parameters employed for tenofovir were $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and $C_{max}$.<br>The mean ± SD values of primary pharmacokinetic parameters of tenofovir for Test Product-T and Reference Product-R for thirty-nine subjects were summarized in the following table : |

| **Parameters (Units)** | **(Un-transformed data)** | |
|---|---|---|
| | **Test-T** | **Reference -R** |
| $AUC_{0\text{-tlast}}$ (ng.hr/mL) | 2593.154 ± 718.2925 | 2570.191 ± 663.5471 |
| $AUC_{0\text{-}\infty}$ (ng.hr/mL) | 2826.262 ± 728.3133 | 2790.606 ± 669.7772 |
| $C_{max}$ (ng/mL) | 319.076 ± 94.7497 | 331.013 ± 87.8408 |

## 2. STUDY SYNOPSIS (Continued)

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|---|---|
| **Generic Name:** Tenofovir<br>**Test Product:** Tenevir 300 mg Tablets<br>**Reference Product:** Viread™ 300 mg Tablets | **Sponsor's Name:**<br>The Government Pharmaceutical Organization |
| **Secondary Pharmacokinetic Parameters:** | The secondary pharmacokinetic parameters employed for tenofovir were $T_{max}$, $\lambda_z$, $t_{1/2}$, $AUC_{0\text{-tlast}}$/ $AUC_{0\text{-}\infty}$ and AUC_%Extrap_obs.<br>The mean ± SD values of secondary pharmacokinetic parameters of tenofovir for Test Product-T and Reference Product-R for thirty-nine subjects were summarized in the following table : |

| Parameters (Units) | (Un-transformed data) | |
|---|---|---|
| | Test-T | Reference -R |
| $T_{max}$ (hr)* | 0.833 (0.500,2.000) | 0.667 (0.500,1.500) |
| $\lambda_z$ (1 / hr) | 0.040 ± 0.0061 | 0.040 ± 0.0062 |
| $t_{½}$ (hr) | 17.825 ± 2.5213 | 17.581 ± 2.6099 |
| $AUC_{0\text{-tlast}}$ / $AUC_{0\text{-}\infty}$ | 0.913 ± 0.0375 | 0.917 ± 0.0350 |
| AUC_%Extrap_obs (%) | 8.664 ± 3.7472 | 8.302 ± 3.4965 |

*$T_{max}$ were represented in median (Min, Max) value.

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| **PK Confidence Intervals:** | The 90% parametric confidence intervals were calculated for the ln-transformed primary pharmacokinetic parameters, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ of tenofovir (N=39) and presented as below. |

| Parameters | Ratios | 90% CI |
|---|---|---|
| ln $AUC_{0\text{-tlast}}$ | 101.0 | 97.70-104.48 |
| ln $AUC_{0\text{-}\infty}$ | 101.4 | 98.16-104.80 |
| ln $C_{max}$ | 96.0 | 90.14-102.27 |

## 2. STUDY SYNOPSIS (Continued)

| | | |
|---|---|---|
| **Generic Name:** | Tenofovir | **Sponsor's Name:** The Government Pharmaceutical Organization |
| **Test Product:** | Tenevir 300 mg Tablets | |
| **Reference Product:** | Viread™ 300 mg Tablets | |
| **Conclusion:** | | The Test Product-T (Tenevir 300 mg Tablets – Manufactured by: GPO, Thailand/ Batch No. S550622) when compared with the Reference Product-R (Viread™ 300 mg Tablets – Manufactured by: Nycomed GmbH, Oranienburg, Germany, Manufactured for Gilead Science, Inc. Foster City, California, USA./ Batch No. W178485D) meets the bioequivalence criteria (90% confident interval for the ratio of geometric least squares means within 80.00-125.00%) with respect to the rate and extent of absorption of tenofovir as set in the protocol. |
| **Date of Report:** | | 04 Feb 2015 |