2. STUDY SYNOPSIS

Generic Name: Efavirenz	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product: Efavirenz GPO 600 mg Tablets	
Reference Product: Stocrin® 600 mg Tablets	
Study Title:	Comparative Randomized, Single Dose, Two-Way Crossover, Open-Label Study to Determine the Bioequivalence of Efavirenz Formulations, Efavirenz GPO 600 mg Tablets and Stocrin® 600 mg Tablets, After Oral Administration to Healthy Thai Volunteers under Fasting Conditions
Investigators:	**Study Director** Dr. Isariya Techatanawat, B.Sc., Ph.D.
	Principal Investigator: Professor Dr. Punnee Pitisuttithum, M.D., MBBS, D.T.M.&H, FRCPT
	Clinical Investigator: Asst. Prof. Jittima Dhitavat, M.D. Asst. Prof. Vipa Thanachartwet, M.D. Assoc. Prof. Varunee Desakorn Dr. Viravarn Luvira, M.D.
	Analytical Investigator: Dr. Bancha Chuasuwan, B.Sc., Ph.D.(Pharm)
	PK & Statistical Investigator: Ms. Busarat Karachot, , M.Sc. (Pharmacology)
Project Number:	BE005-14
Protocol Number:	P004-14

2. STUDY SYNOPSIS (Continued)

Generic Name: Efavirenz **Test Product:** Efavirenz GPO 600 mg Tablets **Reference Product:** Stocrin® 600 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
IEC/IRB Approval Date:	Ethics Committee of the Faculty of Tropical Medicine, Mahidol University 420/6 Ratchawithi Rd. Ratchathewi, Bangkok, Thailand 10400 Phone no. +66 2 3549100-19 # 1535, 1349 Fax no. + 66 2 3069126 Approval Date: 30 Apr 2014 (for period from 25 Apr 2014 to 24 Apr 2015) Protocol version 02, dated 20 Mar 2014
Objectives:	To compare the rate and extent of absorption of efavirenz from efavirenz formulation with that of reference formulation. 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):** Efavirenz GPO (Efavirenz) 600 mg Tablets Each film coated tablet contains efavirenz 600 mg Manufactured by: The Government Pharmaceutical Organization, Bangkok, Thailand. Batch No. S560073 Mfg. Date 25 Mar 2013 Exp. Date 25 Mar 2015

2. STUDY SYNOPSIS (Continued)

Generic Name: Efavirenz **Test Product:** Efavirenz GPO 600 mg Tablets **Reference Product:** Stocrin® 600 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Dosage Regimen (continued):	**Reference Product (R):** Stocrin® (Efavirenz) 600 mg Tablets Each film coated tablet contains efavirenz 600 mg. Manufactured by: Merck Sharp & Dohme (Australia) Pty. Limited, South Granville, N.S.W., Australia. Marketing Authorization Holder: MSD (Australia) Ltd., Bangkok, Thailand. Batch No. V1626 Mfg. Date 05 Dec 2012 Exp. Date 05 Dec 2014
Clinical Study Site:	Bioequivalence unit, Faculty of Tropical Medicine, Mahidol University 420/6 Ratchawithi road, Ratchathewi, Bangkok, Thailand 10400
Study Subjects:	36 subjects, selected randomly from healthy adult Thai male volunteers. No. of subjects enrolled: 36 No. of subjects withdrawn/ dropped out: 0 No. of subjects completed: 36 No. of subjects analyzed: 36 No. of subjects included in pharmacokinetics: 36 No. of subjects included in statistical analysis: 36
Demographic Data (N=36):	Age 27.1±6.5 year ; Height 169.9± 4.4 cm; Weight 63.6±6.6 kg ; BMI 22.0±1.9 kg/m^2

2. STUDY SYNOPSIS (Continued)

Generic Name: Efavirenz **Test Product:** Efavirenz GPO 600 mg Tablets **Reference Product:** Stocrin® 600 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Admission and Confinement:	Subjects were housed in the clinical facility for four nights and five days in each period (including 2 periods of the study for eight nights and ten days). The subjects stayed for one night or at least 10.0 hours in facility prior to IMP administration until 72.0 hours after dosing in each period. In case of any adverse event, necessary action would be taken till event subsides.
Drug Administration:	After an overnight fast of at least 10.0 hours, one tablet of efavirenz 600 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: 16 May 2014 – 23 May 2014 Period I: 26 May 2014 – 30 May 2014 Period II: 23 Jun 2014 – 27 Jun 2014
Washout Period:	28 days between period I and period II

2. STUDY SYNOPSIS (Continued)

Generic Name: Efavirenz **Test Product:** Efavirenz GPO 600 mg Tablets **Reference Product:** Stocrin® 600 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Blood Sampling Schedule:	A total of 19 blood samples, each of 05 mL (07 mL in case of pre dose sample) were collected from each subject in each period. The venous blood samples were withdrawn at pre-dose (0.000) and 1.000, 2.000, 2.500, 3.000, 3.500, 4.000, 4.500, 5.000, 5.500, 6.000, 6.500, 7.000, 8.000, 10.000, 12.000, 24.000, 48.000 and 72.000 hours post-dose following drug administration. 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. For each subject, combining the two periods, the total volume of blood drawn would be 246±10 mL.
Blood Sampling Handling:	Blood samples were placed in a refrigerated centrifuge within 30 minutes from the time of collection and centrifuged. The blood samples were centrifuged at 3000 ± 100 rcf for 5 minutes below 10°C to separate plasma.

2. STUDY SYNOPSIS (Continued)

Generic Name: Efavirenz **Test Product:** Efavirenz GPO 600 mg Tablets **Reference Product:** Stocrin® 600 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Blood Sampling Handling (continued):	The blood samples were kept in wet ice water bath before centrifugation and during separation. The separated plasma was transferred to prelabeled polypropylene tubes in two aliquots [around 0.8 mL in first lot (around 1.2 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. 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. 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)

<table>
<tr><td>Generic Name: Efavirenz
Test Product: Efavirenz GPO 600 mg Tablets
Reference Product: Stocrin® 600 mg Tablets</td><td>Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Clinical Sample Storage:</td><td>Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization.</td></tr>
<tr><td>Analytical Site:</td><td>Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization.</td></tr>
<tr><td>Bioanalytical Methodology:</td><td>Plasma samples of subjects were assayed for efavirenz using a validated LC-MS/MS method.</td></tr>
<tr><td>Analyte:</td><td>Plasma efavirenz concentration</td></tr>
<tr><td>Safety Evaluation:</td><td>Both treatments were well tolerated. No clinically significant or serious ADR were observed</td></tr>
<tr><td>Surrogate Parameters:</td><td>Drug plasma concentrations to indicate clinical activity.</td></tr>
<tr><td>Primary Pharmacokinetic Parameters:</td><td>The primary pharmacokinetic parameters employed for efavirenz were AUC_{0-72} and C_{max}.
The mean ± SD values of primary pharmacokinetic parameters of efavirenz for Test Product-T and Reference Product-R for thirty-six subjects were summarized in the following table :
<table>
<tr><th rowspan="2">Parameters (Units)</th><th colspan="2">(Un-transformed data)</th></tr>
<tr><th>Test-T</th><th>Reference -R</th></tr>
<tr><td>AUC_{0-72} (ng.hr/mL)</td><td>72786.731 ± 22733.8560</td><td>75961.240 ± 19221.2167</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>2872.246 ± 1030.9529</td><td>3201.966 ± 940.4818</td></tr>
</table>
</td></tr>
</table>

2. STUDY SYNOPSIS (Continued)

<table>
<tr><td>Generic Name: Efavirenz
Test Product: Efavirenz GPO 600 mg Tablets
Reference Product: Stocrin® 600 mg Tablets</td><td>Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Secondary Pharmacokinetic Parameters:</td><td>The secondary pharmacokinetic parameters employed for efavirenz were T_{max}.
The median (Min, Max) value of secondary pharmacokinetic parameters of efavirenz for Test Product-T and Reference Product-R for thirty-six subjects were summarized in the following table :
<table>
<tr><th rowspan="2">Parameters (Units)</th><th colspan="2">(Un-transformed data)</th></tr>
<tr><th>Test-T</th><th>Reference -R</th></tr>
<tr><td>T_{max} (hr)</td><td>3.500 (2.000,8.000)</td><td>3.500 (1.000,6.000)</td></tr>
</table></td></tr>
<tr><td>PK Confidence Intervals:</td><td>The 90% parametric confidence intervals were calculated for the ln-transformed primary pharmacokinetic parameters, AUC_{0-72} and C_{max} of efavirenz (N=36) and presented as below.
<table>
<tr><th>Parameters</th><th>Ratios</th><th>90% CI</th></tr>
<tr><td>ln AUC_{0-72}</td><td>98.3</td><td>91.55-105.59</td></tr>
<tr><td>ln C_{max}</td><td>92.3</td><td>83.85-101.62</td></tr>
</table></td></tr>
</table>

2. STUDY SYNOPSIS (Continued)

Generic Name:	Efavirenz	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Efavirenz GPO 600 mg Tablets	
Reference Product:	Stocrin® 600 mg Tablets	
Conclusion:		The Test Product-T (Efavirenz GPO 600 mg Tablets – Manufactured by: GPO, Thailand/ Batch No. S560073) when compared with the Reference Product-R (Stocrin® 600 mg Tablets – Manufactured by: Merck Sharp & Dohme (Australia) Pty. Limited, South Granville, N.S.W., Australia/ Batch No. V1626) 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 efavirenz as set in the protocol.
Date of Report:		07 Jan 2015