Protocol No. ARL/11/205

Study No. ARL/11/205

STUDY TITLE: A Randomized, Balanced, Open Label, Two-Sequence, Two-Treatment, Two-Period, Single Dose, Crossover, Bioequivalence Study of Efavirenz 600 mg Tablets of The Government Pharmaceutical Organization, Thailand., with STOCRIN® (Efavirenz) 600 mg Tablets of MSD, Australia., in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions

FINAL STUDY REPORT

Principal Investigator: Dr. Suhas Khandave, M.D. (Pharmacology) Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21	**Sponsor:** The Government Pharmaceutical Organization 75/1 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand
Clinical Investigator: Dr. Vivekananda Murthi, M.B.B.S. Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21	**Analytical Investigator:** Dr. Ashutosh Pudage, Ph.D Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21
Clinical Laboratory Investigator: Dr. Gurmeet Singh, M.D. (Pathology) Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21	**Pharmacokinetic and Statistic Investigator:** Dr. Nand Kishore Rawat, Ph.D Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21
Clinical Facility Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21	**Analytical Facility** Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21
IRC/EC Approval Date: Drushti Independent Ethics Committe, Approval Date 18 Jul 2011	
Clinical Study Date: Period I: 19 Aug 2011 to 23 Aug 2011 Period II:17 Sep 2011 to 21 Sep 2011	
Analytical Study Date: 04 Oct 2011 to 20 Oct 2011	
Approved Signatures: **Principal Investigator:**.....**Date**.....11../..12...../.....12 **Clinical Investigator:**.....**Date**.....11.../...12...../...12... **Analytical Investigator:**.....**Date**.....11.../....12.../....12 **PK & Statistic Investigator:**.....**Date**.....11../....12...../..12.....	

Compliance Statement

Protocol No. ARL/11/205	Study No. ARL/11/205

Study Title:

A Randomized, Balanced, Open Label, Two-Sequence, Two-Treatment, Two-Period, Single Dose, Crossover, Bioequivalence Study of Efavirenz 600 mg Tablets of The Government Pharmaceutical Organization, Thailand., with STOCRIN® (Efavirenz) 600 mg Tablets of MSD, Australia., in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions

Phases of study	Address
Clinical, Bio-analytical and Statistical	Accutest Research Laboratories (I) Pvt. Ltd., A-31, MIDC, TTC Industrial Area Khairane, Navi Mumbai 400 709 Maharashtra, India Tel. No. +91-22-2778 0718 Fax No. +91-22-2778 0718

The study was carried out in accordance with the Clinical Research Guidelines established by the "Declaration of Helsinki" and in compliance with the protocol and in accordance with Good Clinical Practices (GCP) as described in the ICH Harmonized Tripartite Guidelines for GCP E6 (R1) 1996 and applicable Regulatory Authority guidelines.

The bio-analytical section the study was performed in compliance with Protocol, Standard Operating Procedures and in accordance with applicable principles of Good Laboratory Practices (GLP).

We, the undersigned, declare that we have reviewed this report for completeness, accuracy and compliance with protocol, SOPs, Good Clinical Practices/Good Laboratory Practices and applicable Regulatory Authority guidelines. This study report accurately reflects the raw data and also audited by Independent Quality Assurance department for accuracy.

Dr. Suhas Khandave **Principal Investigator**	Signature	11/12/12 Date
Dr. Ashutosh Pudage **Analytical Investigator**	Signature	11/12/12 Date
Dr. Nand Kishore Rawat **Pharmacokinetic and Statistic Investigator**	for Richara Signature	11/12/12 Date

Quality Assurance Statement

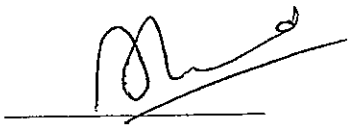
Protocol No. ARL/11/205	Study No. ARL/11/205

The study was conducted in accordance with GCP, applicable principles of GLP, Protocol, SOPs and applicable Regulatory Authority guidelines and the final report accurately describe the study methods and procedures used and the reported results accurately reflect the raw data.

I, the undersigned, declare that we have reviewed this report for completeness, accuracy and compliance with protocol, SOPs and Good Clinical Practices/Good Laboratory Practices and applicable Regulatory Authority guidelines. This study report accurately reflects the raw data and also audited by Independent Quality Assurance department for accuracy

Dr. Avdhoot Laud

Head of Quality Assurance



Signature

11/12/12

Date

2. STUDY SYNOPSIS

Generic Name: Efavirenz **Test Product:** Efavirenz **Reference Product:** STOCRIN®	**Sponsor's Name:** The Government Pharmaceutical Organization
Study Title:	A Randomized, Balanced, Open Label, Two-Sequence, Two-Treatment, Two-Period, Single Dose, Crossover, Bioequivalence Study of Efavirenz 600 mg Tablets of The Government Pharmaceutical Organization, Thailand., with STOCRIN® (Efavirenz) 600 mg Tablets of MSD, Australia., in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions
Investigators:	Principal Investigator: Dr. Suhas Khandave, M.D. (Pharmacology) Clinical Investigator: Dr. Vivekananda Murthi, M.B.B.S. Analytical Investigator: Dr. Ashutosh Pudage, Ph.D PK & Statistic Investigator: Dr. Nand Kishore Rawat, Ph.D
Protocol Number:	ARL/11/205
Study Number:	ARL/11/205
IRC/Ethics Approval Date:	Drushti Independent Ethics Committe, Approval Date 18 Jul 2011
Objectives:	To demonstrate the bioequivalence between **Test Product:** Efavirenz 600 mg Tablets of The Government Pharmaceutical Organization, Thailand., and **Reference Product:** STOCRIN® (Efavirenz) 600 mg Tablets of MSD, Australia., in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions To monitor the safety and tolerability of a single dose of Efavirenz 600 mg Tablets in normal, healthy, adult, male and female human subjects.

2. STUDY SYNOPSIS (Cont.)

Generic Name: Efavirenz **Test Product:** Efavirenz **Reference Product:** STOCRIN®	**Sponsor's Name:** The Government Pharmaceutical Organization
Dosage Regimen:	**Test Product:** Single dose, 600 mg of Efavirenz Tablets Lot No.: S540151, Mfg. Date: 16 Jun 2011, Exp. Date: 16 Jun 2013 **Reference Product:** Single dose, 600 mg of STOCRIN® (efavirenz) Tablet Lot No.: S0424, Mfg. Date: 21 Jan 2011, Exp. Date: 21 Jan 2013
Clinical Study Site:	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21 Fax no. + 91 22 2778 0720
Study Subjects:	No. of subjects enrolled: 36 normal, healthy, adult, male human subjects No. of subjects dropped out: 05 No. of subjects completed: 31 No. of subjects analyzed: 31 Subject no. 5 showed pre-dose concentration greater than 5 % of C_{max} in period II. Hence, the subject was not considered for pharmacokinetic and statistical analysis. No. of subjects included in pharmacokinetics and statistical analysis: 30
Demographic Data of Enrolled Subjects (N=36):	Age = 28.42 ± 4.97 year; Height = 165.44 ± 4.66 cm; Weight 61.47 ±8.14 kg, BMI 22.45 ± 2.73 kg/m^2
Demographic Data of subjects included in pharmacokinetics and statistical analysis (N=30):	Age = 27.87 ± 4.78 year; Height = 165.60 ± 4.09 cm; Weight 61.67 ± 8.49 kg, BMI 22.46 ± 2.79 kg/m^2

2. STUDY SYNOPSIS (Cont.)

Generic Name: Efavirenz **Test Product:** STOCRIN® **Reference Product:** Efavirenz	**Sponsor's Name:** The Government Pharmaceutical Organization
Admission and Confinement:	Subjects were admitted the night before study drug administration. Subjects were confined at least 10.50 hours prior to study drug administration and until 24.00 hours post dose in each study period.
Drug Administration:	A single dose of Efavirenz Tablets 600 mg was administered along with 240 mL of drinking water.
Study Period:	**Screening:** 01- 05 Aug 2011, 10 Aug 2011, 12-13 Aug 2011 and 16-19 Aug 2011 **Enrollment:** Period I: 19 Aug 2011 to 23 Aug 2011 Period II:17 Sep 2011 to 21 Sep 2011
Washout Period:	29 days 20 Aug 2011 to 18 Sep 2011
Blood Sampling Schedule:	A total of 19 blood samples were drawn at pre dose (within 1 hr prior to dosing) and at 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours post dose. Total blood loss in this study was approximately 254.8 mL.
Blood Sampling Handling:	The blood sample for Efavirenz were placed in sodium heparin vacutainer, centrifuged under refrigeration with the machine set at 3500 RPM and 5°C, for 10 minutes.
Clinical Sample Storage:	The separating plasma samples were stored in deep freezer maintained at -70°C ± 10°C until analyzed.

Generic Name: Efavirenz **Test Product:** Efavirenz **Reference Product:** STOCRIN®	**Sponsor's Name:** The Government Pharmaceutical Organization
Analytical Site:	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709 Phone no. + 91 22 2778 0718/19/21 Fax no. + 91 22 2778 0720
Bioanalytical Methodology:	Plasma Samples were analyzed for Efavirenz using Validated LC-MS/MS method., LLOQ = 50.262 ng/ml
Analyte:	Plasma Efavirenz concentration
Safety Evaluation:	A total of twenty-three adverse events were reported during the study. The adverse events were mild in severity and were resolved. Twenty adverse events were expected and definitely related to the study drug and three adverse events were unexpected and unrelated to the study drug. No serious adverse events were observed during both the periods of the study.
Surrogate Parameters:	Drug plasma concentrations to indicate clinical activity.

<table>
<tr><td>Generic Name: Efavirenz
Test Product: Efavirenz
Reference Product: STOCRIN®</td><td>Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Primary Pharmacokinetic Parameters:</td><td>The primary pharmacokinetic parameter employed for Efavirenz was C_{max} and AUC_{0-72}.
The mean ± SD values of primary pharmacokinetic parameters of Efavirenz for Test Product-A and Reference Product-B for thirty subjects are summarized in the following table:
<table>
<tr><th rowspan="2">Parameters (Unit)</th><th colspan="2">Mean ± SD
(Un-transformed data)</th></tr>
<tr><th>Test Product-A</th><th>Reference Product-B</th></tr>
<tr><td>AUC_{0-72} (ng.hr/mL)</td><td>69701.29±22631.94</td><td>66865.85±23885.05</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>2926.79±782.30</td><td>2767.20±744.51</td></tr>
</table></td></tr>
<tr><td>Secondary Pharmacokinetic Parameters:</td><td>The secondary pharmacokinetic parameter employed for Efavirenz was T_{max}. The mean ± SD values of secondary pharmacokinetic parameter of Efavirenz for Test Product-A and Reference Product-B for thirty subjects are summarized in the following table:
<table>
<tr><th rowspan="2">Parameters (Units)</th><th colspan="2">Mean ± SD
(Un-transformed data)</th></tr>
<tr><th>Test Product-A</th><th>Reference Product-B</th></tr>
<tr><td>T_{max} (hrs)</td><td>3.30± 0.95</td><td>3.37± 1.11</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Generic Name: Efavirenz
Test Product: Efavirenz
Reference Product: STOCRIN®</td><td>Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>PK Confidence Intervals:</td><td>The 90% parametric confidence intervals were calculated for the ln-transformed primary pharmacokinetic parameters, C_{max} and AUC_{0-72} of the Efavirenz and presented as below.
<table>
<tr><th>Parameter</th><th>Ratio</th><th>90% CI</th></tr>
<tr><td>C_{max}</td><td>105.4865</td><td>95.4687-116.5554</td></tr>
<tr><td>AUC_{0-72}</td><td>104.4011</td><td>97.5355-111.7501</td></tr>
</table></td></tr>
<tr><td>Conclusion:</td><td>Point estimates and the 90% confidence intervals for the log-transformed ratios (Test/Reference) for the C_{max} and AUC_{0-72} were within the 80.00-125.00. Therefore, the bioequivalence of Efavirenz 600 mg Tablets of The Government Pharmaceutical Organization, Thailand, and STOCRIN® (Efavirenz) 600 mg Tablets of MSD, Australia., can be concluded.</td></tr>
<tr><td>Date of Report:</td><td>11 December 2012</td></tr>
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