Protocol No BEGPO 04/2011

Study No. BEGPO-01/2012

STUDYTITLE: Bioequivalence study of Tenofovir 300 mg + Emtricitabine 200 mg tablet in healthy Thai volunteers

FINAL STUDY REPORT

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Clinical Investigator: Dr.Archawin Rojanawiwat, M.D.Ph.D. Clinical Research Center, Department of Medical Sciences, Ministry of Public Health, Thiwanon Rd., Amphur Mueng, Nontaburi, Thailand 11000 Phone no.+662 9510000-9 ext 98465,98464 Fax no. +662 9659756	**Analytical Investigator:** Dr. Ashutosh Pudage, Ph.D. Accutest Research Laboratories (I) Pvt. Ltd., A-91 M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709, India Phone no. + 91 22 2778 0718/19/21 Fax no. + 91 22 2778 0720
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IRC/EC Approval Date: Institute for Development of Human Research Protection (IHRP) 19 Jul 2011, 26 Aug 2011 (1st amendment), 23 Sep 2011 (minor amendment)	
Clinical Study Date: 05 Dec – 30 Dec 2011	
Analytical Study Date: 09 Jan - 13 Feb 2012	

Approved Signatures:

Principal Investigator:.....**Date**...../...../.....

Clinical Investigator:.....**Date**...../...../.....

Analytical Investigator:.....**Date**...01../...10...../...12...

PK & Statistic Investigator:.....**Date**...01../...10...../...12...

Other Investigator: .....**Date**...../...../.....

Compliance Statement

Protocol No. BEGPO 04/2011

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We attest to the fact that the data presented here is accurate and reflects the raw data. The study has been conducted as per the protocol, ICH 'Guidance on Good Clinical Practice', Declaration of Helsinki, Principles of Good Laboratory Practice and SOPs of Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization, Clinical Research Center, Department of Medical Sciences, Ministry of Public Health and Accutest Research Laboratories (I) Pvt. Ltd.,/India and we, on behalf of Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization, accept the responsibility for scientific correctness of the project and the validity of the data produced in this report. All essential documents pertaining to the study are available in the archives.

Dr.Isariya Techatanawat	_____	___/___/___
Principal Investigator	Signature	Date
Dr.Archawin Rojanawiwat	_____	___/___/___
Clinical Investigator	Signature	Date
Dr. Ashutosh Pudage	_____	01/10/12
Analytical Investigator	Signature	Date
Dr. Nand Kishore Rawat	_____	01/10/12
Pharmacokinetic and Statistic Investigator	Signature	Date
Ms.Achara Eksaengsri	_____	___/___/___
Other Investigator	Signature	Date

Quality Assurance Statement

Protocol No. BEGPO 04/2011

Study No. BEGPO-01/2012

The raw data have been reviewed and all phases of the study have been inspected by quality assurance team for compliance with applicable Good Clinical Practice (GCP), Good Laboratory Practices (GLP) in addition to the Standard Operating Procedures (SOPs) of Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization. The results reported herein accurately reflect raw data of all phased of the study.

Dr.Nuntakan Suwanpidokkul	_____	____/____/____
Quality Assurance Team	Signature	Date
Dr.Yaowapa Suvathi	_____	____/____/____
Head of Quality Assurance Team	Signature	Date

2. STUDY SYNOPSIS

Generic Name:	Tenofovir 300 mg +Emtricitabine 200 mg tablet
Test Product:	TENO-EM
Reference Product:	Truvada®
Sponsor's Name:	The Government Pharmaceutical Organization
Study Title:	Bioequivalence study of Tenofovir 300 mg + Emtricitabine 200 mg tablet in hlealthy Thai volunteer
Investigators:	Principal Investigator: Dr.Isariya Techatanawat Clinical Investigator: Dr.Archawin Rojanawiwat Analytical Investigator: Dr. Ashutosh Pudage PK & Statistic Investigator: Dr. Nand Kishore Rawat Other Investigator: Ms.Achara Eksaengsri
Protocol Number:	BEGPO 04/2011
Study Number:	BEGPO-01/2012
IRC/Ethics Approval Date:	Institute for Development of Human Research Protection 19 Jul 2011, 26 Aug 2011 (1st amendment), 23 Sep 2011 (minor amendment)
Objectives:	To compare the rate and extent of absorption of a Tenofovir 300 mg + Emtricitabine 200 mg tablet formulation with those of a reference formulation (Truvada®) when given a single dose under fasting conditions. To investigate the safety and tolerability of the formulations on the basis of clinical and laboratory examinations at the beginning and at the end of the trial and registration of adverse events and/or adverse drug reactions.
Dosage Regimen:	Test Product: Single dose TENO-EM Tablet (Tenofovir 300 mg + Emtricitabine 200 mg). Batch No. S530463 Mfg. Date 20 Sep 2010 Exp. Date 20 Sep 2012 Reference Product: Single dose, Truvada®Tablet (Tenofovir 300 mg + Emtricitabine 200 mg). Batch No. L117707 Mfg. Date Apr 2009 Exp. Date Apr 2012

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir 300 mg +Emtricitabine 200 mg tablet
Test Product:	TENO-EM
Reference Product:	Truvada®
Sponsor's Name:	The Government Pharmaceutical Organization
Clinical Study Site:	Clinical Research Center, Department of Medical Sciences, Ministry of Public Health, 88/7 Tiwanond rd. Nonthaburi 11000, Thailand
Study Subjects:	Forty-six subjects plus four alternatives, selected randomly from healthy adult Thai male volunteers.
Demographic Data (N=50):	Age = 30.38±7.46 year; Height = 171.70±6.73 cm; Weight= 65.82±7.30 kg, BMI= 22.29±1.77 kg/m^2
Admission and Confinement:	Subjects were admitted the night before study drug administration, supervised for at least 10.0 hrs overnight fasting and confined until collecting the 24.0 hrs sample.
Drug Administration:	Each subject randomly received a single dose of the assigned formulation, administered with 240 ml of water.
Study Period:	Screening: 15 – 17 Nov 2011 Enrollment: 5 – 30 Dec 2011 Group A: Period I: 5 – 9 Dec 2011 Period II: 12 – 16 Dec 2011 Group B : Period I: 19 – 23 Dec 2011 Period II 26 – 30 Dec 2011
Washout Period:	7 days
Blood Sampling Schedule:	22 blood samples were drawn at 0.00 (pre-dose sample) and 0.16, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, 48.0 and 72.0 hours (post-dose). The total volume of blood draw did not exceeded 292 ml.

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir 300 mg +Emtricitabine 200 mg tablet	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	TENO-EM	
Reference Product:	Truvada®	
Blood Sampling Handling:		The blood sample for Tenofovir+Emtricitabine were placed in Sodium Heparin tubes, centrifuged, and the separating plasma samples were immediately stored at below -50 °C or colder until analyzed.
Clinical Sample Storage:		Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization
Analytical Site:		Accutest Research Laboratories, (I) Pvt. Ltd., A-91, M.I.D.C, T.T.C Industrial Area, Khairane, Navi Mumbai –400709, India Phone no. + 91 22 2778 0718/19/21 Fax no. + 91 22 2778 0720
Bioanalytical Methodology:		Plasma samples of subjects were assayed for Tenofovir and Emtricitabine using a validated LC-MS / MS method., LLOQ= 50 ng/ml
Analyte:		Plasma Tenofovir+Emtricitabine concentration
Safety Evaluation:		Both treatments were well tolerated and none of clinically significant or serious ADR observe through the study period.
Surrogate Parameters:		Drug plasma concentrations to indicate clinical activity.

2. STUDY SYNOPSIS (Cont.)

<table>
<tr><td>Generic Name:</td><td>Tenofovir 300 mg +Emtricitabine 200 mg tablet</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product:</td><td>TENO-EM</td></tr>
<tr><td>Reference Product:</td><td>Truvada®</td></tr>
<tr><td>Primary Pharmacokinetic Parameters:</td><td colspan="2">The primary pharmacokinetic parameter employed for Tenofovir was $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}.
The mean ± SD values of primary pharmacokinetic parameters of Tenofovir for Test Product-A and Reference Product-B for Fifty 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>$AUC_{0\text{-tlast}}$ (ng.hr(/mL)</td><td>2193.54±534.78</td><td>2197.68±554.57</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng.hr/mL)</td><td>2544.90±549.97</td><td>2548.97±551.02</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>333.06±82.56</td><td>346.98±97.88</td></tr>
</table></td></tr>
</table>

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir 300 mg +Emtricitabine 200 mg tablet
Test Product:	TENO-EM
Reference Product:	Truvada®
Sponsor's Name:	The Government Pharmaceutical Organization

Primary Pharmacokinetic Parameters:

The primary pharmacokinetic parameter employed for Emtricitabine was $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}.

The mean ± SD values of primary pharmacokinetic parameters of Emtricitabine for Test Product-A and Reference Product-B for Fifty subjects are summarized in the following table:

Parameters (Unit)	Mean ± SD (Un-transformed data)	
	Test Product-A	Reference Product-B
$AUC_{0\text{-}tlast}$ (ng.hr/mL)	8937.09±1674.31	8793.21±1679.79
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	9561.41±1716.40	9455.86±1689.24
C_{max} (ng/mL)	2304.59±623.43	2331.42±778.91

2. STUDY SYNOPSIS (Cont.)

<table>
<tr><td>Generic Name:</td><td>Tenofovir 300 mg +Emtricitabine 200 mg tablet</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product:</td><td>TENO-EM</td></tr>
<tr><td>Reference Product:</td><td>Truvada®</td></tr>
<tr><td>Secondary Pharmacokinetic Parameters:</td><td colspan="2">The secondary pharmacokinetic parameter employed for Tenofovir was T_{max}, K_{el}, $t_{1/2}$, AUC_%Extrap_obs and AUC-ratio. The mean ± SD values of secondary pharmacokinetic parameters of Tenofovir for Test Product-A and Reference Product-B for Fifty 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>T_{max} (hr)</td><td>0.81±0.32</td><td>0.93±0.46</td></tr>
<tr><td>K_{el} (hr^{-1})</td><td>0.05±0.01</td><td>0.05±0.01</td></tr>
<tr><td>$t_{½}$ (hr)</td><td>14.76±3.23</td><td>14.84±3.11</td></tr>
<tr><td>AUC_%Extrap_obs (%)</td><td>14.32±4.41</td><td>14.55±5.43</td></tr>
<tr><td>Ratio ($AUC_{0\text{-}tlast}$ / $AUC_{0\text{-}\infty}$)</td><td>85.68±4.41</td><td>85.45±5.43</td></tr>
</table></td></tr>
</table>

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Tenofovir 300 mg +Emtricitabine 200 mg tablet
Test Product:	TENO-EM
Reference Product:	Truvada®

Sponsor's Name:

The Government Pharmaceutical Organization

Secondary Pharmacokinetic Parameters:

The secondary pharmacokinetic parameter employed for Emtricitabine was T_{max}, K_{el}, $t_{1/2}$, AUC_%Extrap_obs and AUC-ratio. The mean ± SD values of secondary pharmacokinetic parameters of Emtricitabine for Test Product-A and Reference Product-B for Fifty subjects are summarized in the following table:

Parameters (Unit)	Mean ± SD (Un-transformed data)	
	Test Product-A	Reference Product-B
T_{max} (hr)	1.13±0.29	1.29±0.58
λ_z (hr^{-1})	0.22±0.05	0.22±0.05
$t_{½}$ (hr)	3.45±1.18	3.40±1.11
AUC_%Extrap_obs (%)	6.63±1.53	7.26±3.01
Ratio ($AUC_{0-tlast}$ / $AUC_{0-\infty}$)	93.37±1.53	92.74±3.01

2. STUDY SYNOPSIS (Cont.)

<table>
<tr><td>Generic Name:</td><td>Tenofovir 300 mg +Emtricitabine 200 mg tablet</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product:</td><td>TENO-EM</td></tr>
<tr><td>Reference Product:</td><td>Truvada®</td></tr>
<tr><td colspan="2">PK Confidence Intervals:</td><td>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 the Tenofovir and presented as below.
<table>
<tr><th>Parameter</th><th>Ratio</th><th>90% CI</th></tr>
<tr><td>ln $AUC_{0\text{-tlast}}$</td><td>100.1469</td><td>94.8875- 105.6979</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>99.8084</td><td>95.5446- 104.2624</td></tr>
<tr><td>ln C_{max}</td><td>96.2056</td><td>90.4371- 102.3421</td></tr>
</table>
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 the Emtricitabine and presented as below.
<table>
<tr><th>Parameter</th><th>Ratio</th><th>90% CI</th></tr>
<tr><td>ln $AUC_{0\text{-tlast}}$</td><td>102.2188</td><td>98.4475- 106.1345</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>101.4604</td><td>98.1631- 104.8685</td></tr>
<tr><td>ln C_{max}</td><td>101.4182</td><td>94.9481- 108.3293</td></tr>
</table></td></tr>
<tr><td colspan="2">Conclusion:</td><td>The 90% confidence intervals for the log-transformed ratios (Test/Reference) for the $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} were within the range of 80% to 125 % for Tenofovir and Emtricitabine. Therefore, the bioequivalence of Test Product: Single dose TENO-EM Tablet (Tenofovir 300 mg + Emtricitabine 200 mg) and Reference Product: Single dose, Truvada®Tablet (Tenofovir 300 mg + Emtricitabine 200 mg) can be concluded.</td></tr>
<tr><td colspan="2">Date of Report:</td><td>28 September 2012</td></tr>
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