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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 Facility	Analytical Facility
Clinical Research Center	Accutest Research Laboratories (I) Pvt.
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IRC/EC Approval Date: Institute for Developm	nent of Human Research Protection (IHRP)
19 Jul 2011, 26 Aug 2	011 (1" amendment),
23 Sep 2011 (minor ar	nendment)
Clinical Study Date: 05 Dec – 30 Dec 2011	
Analytical Study Date: 09 Jan - 13 Feb 2012	

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Approved Signatures:	
Principal Investigator:	Date/
Clinical Investigator:	Date
Clinical Investigator: Analytical Investigator:	Date 01/10/12.
PK & Statistic Investigator: Fr Ruber	Date
Other Investigator:	

Compliance Statement

Protocol No. BEGPO 04/2011 Study No. BEGPO-01/2012

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 Analytical Investigator	Signature	01/10/12 Date
Dr. Nand Kishore Rawat Pharmacokinetic and	for Archaer Signature	01 /10 / 12 Date
Statistic Investigator	C	
Ms.Achara Eksaengsri		/
Other Investigator	Signature	Date

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Quality Assurance Statement

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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

	Tenofovir 300 mg	Sponsor's Name:
Generic	+Emtricitabine	The Government Pharmaceutical Organization
Name:	200 mg tablet	
Test Product:	TENO-EM	· ·
Reference		
Product:	Truvada [®]	
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 Numl	per:	BEGPO 04/2011
Study Number	:	BEGPO-01/2012
IRC/Ethics Ap	proval 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 Regimo	en:	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

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	Tenofovir 300 mg	Sponsor's Name:
Generic	+Emtricitabine	The Government Pharmaceutical Organization
Name:	200 mg tablet	
Test Product:	TENO-EM	
Reference	Truvada [®]	
Product:	Truvada	
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 I	Data (N=50):	Age = 30.38 ± 7.46 year; Height = 171.70 ± 6.73 cm;
		Weight= $65.82\pm7.30 \text{ kg}$, BMI= $22.29\pm1.77 \text{ kg/m}^2$
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 Administ	ration:	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 Perio	d:	7 days
Blood Samplin	g 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.
<u> </u>		

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Generic	Tenofovir 300 mg	Sponsor's Name:
Name:	+Emtricitabine	The Government Pharmaceutical Organization
	200 mg tablet	
Test Product:	TENO-EM	
Reference	Truvada [®]	
Product:		
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 M	ethodology:	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	on:	Both treatments were well tolerated and none of
		clinically significant or serious ADR observe through the
	•	study period.
Surrogate Parai	meters:	Drug plasma concentrations to indicate clinical activity.

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C	Tenofovir 300 mg	Sponsor's Nam	ie:		
Generic	+Emtricitabine	The Gover	rnment Pharmaceut	ical Organization	
Name:	200 mg tablet				
Test Product:	TENO-EM				
Reference	Truvada [®]				
Product:	Truvada				
Primary Pharn	nacokinetic	The primary pl	harmacokinetic par	rameter employed	for
Parameters:		Tenofovir was A	$\mathrm{AUC}_{0 ext{-tlast}}, \mathrm{AUC}_{0 ext{-}\infty}$ &	and C_{max} .	
		The mean ± S	SD values of prin	nary pharmacokin	netic
		parameters of	Tenofovir for	Test Product-A	and
		Reference Prod	uct-B for Fifty sul	ojects are summari	ized
		in the following	table.		į
			Mean	± SD]
,		Parameters	(Un-transfo		.
		(Unit)	1 est Product-	Reference Product-	ļ
		AUC _{0-t/ast} (ng.hr(/mL)	2193.54±534.78	2197.68±554.57	
		AUC _{0-∞} (ng.hr/mL)	2544.90±549.97	2548.97±551.02	
		C _{max} (ng/mL)	333.06±82.56	346.98±97.88	

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Comonia	Tenofovir 300 mg	Sponsor's Name	•	
Generic	+Emtricitabine	The Govern	ment Pharmaceutica	al Organization
Name:	200 mg tablet			
Test Product:	TENO-EM			
Reference	Truvada [®]		,	
Product:	Tuvada			
Primary Pharn	1acokinetic	The primary pha	armacokinetic parar	meter employed for
Parameters:		Emtricitabine wa	as AUC _{0-tlast} , AUC ₀₋₀	o and C _{max} .
		The mean ± SI	O values of prima	ry pharmacokinetic
		parameters of E	mtricitabine for 7	Test Product-A and
		Reference Produc	ct-B for Fifty subje	cts are summarized
		in the following to	able:	
			i	ı ± SD
•		Parameters	(Un-transfo	rmed data) Reference Product-
	•	(Unit)	A	B
		AUC _{0-tlast} (ng.hr/mL)	8937.09±1674.31	8793.21±1679.79
		AUC _{0∞} (ng.hr/mL)	9561.41±1716.40	9455.86±1689.24
		C _{max} (ng/mL)	2304.59±623.43	2331.42±778.91

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Generic Name:	Tenofovir 300 mg +Emtricitabine	Sponsor's Name: The Government	nt Pharmaceutic	al Organization
	200 mg tablet			
Test Product:	TENO-EM	-	•	
Reference Product:	Truvada [®]			
Secondary Pharm	1acokinetic	The secondary pha	armacokinetic p	arameter employed
Parameters:		for Tenofovir was	T_{max} , K_{ei} , $t_{1/2}$,	AUC_%Extrap_obs
		and AUC-ratio. Th	e mean ± SD v	values of secondary
		pharmacokinetic p	arameters of 7	Tenofovir for Test
		Product-A and Refe	erence Product-	B for Fifty subjects
		are summarized in t	he following tab	ole:
				an ± SD sformed data)
		Parameters (Unit)	Test Product-	Reference Product-
		*	A	В.
		T _{max} (hr)	0.81±0.32	0.93±0.46
		K _{el} (hr - 1)	0.05±0.01	0.05±0.01
		t _½ (hr)	14.76±3.23	14.84±3.11
		AUC_%Extrap_obs (%)	14.32±4.41	14.55±5.43
		Ratio (AUC _{0-tlast} / AUC _{0-∞})	85.68±4.41	85.45±5.43

	Tenofovir 300	Sponsor's Name:	•	
	mg	_	aut Dhamassait	-1 Oiti
Generic Name:	+Emtricitabine	i ne Governin	ent Pharmaceutic	ai Organization
	200 mg tablet			
Test Product:	TENO-EM			
Reference	Truvada [®]			•
Product:				
Secondary Phar	macokinetic	The secondary phar	rmacokinetic par	ameter employed for
Parameters:		Emtricitabine was	Γ_{max} , K_{el} , $t_{1/2}$, AU	JC_%Extrap_obs and
		AUC-ratio. The r	mean \pm SD v	alues of secondary
		pharmacokinetic pa	arameters of En	ntricitabine for Test
		Product-A and Refe	erence Product-B	for Fifty subjects are
		summarized in the fe	ollowing table:	
				n ± SD formed data)
		Parameters (Unit)	Test Product-	Reference Product-
			A	В
		T _{max} (hr)	1.13±0.29	1.29±0.58
		$\lambda_z (hr^{-1})$	0.22±0.05	0.22±0.05
		t _{1/4} (hr)	3.45±1.18	3.40±1.11
		L 3/3 (122)	37.13	3.40±1.11
		AUC_%Extrap_obs (%)	6.63±1.53	7.26±3.01
		AUC_%Extrap_obs		
	·	AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01
	·	AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01
	·	AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01
		AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01
		AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01
	·	AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01
	·	AUC_%Extrap_obs (%) Ratio (AUC _{0-tlast} /	6.63±1.53	7.26±3.01

ļ	Tenofovir 300	Sponsor's Name:		-
	mg	-	Total	
Generic Name:	+Emtricitabine	The Governm	ent Pharmaceutica	l Organization
	200 mg tablet			
Test Product:	TENO-EM	-		
	1ENO-EM	-		
Reference Product:	Truvada [®]			
	T- 4	The 000/ management		vals were calculated
PK Confidence	intervais:	<u> </u>		vais were carculated pharmacokinetic
		i		•
		and presented as bel		max of the Tenofovir
		Parameter	Ratio	90% CI
			100 1460	94.8875- 105.6979
		ln AUC _{0-tlast}	100.1469	
		In AUC _{0-∞}	99.8084	95.5446- 104.2624
		ln C _{max}	96.2056	90.4371-102.3421
		The 90% parametri	c confidence inter	vals were calculated
		for the ln-trans	sformed primary	pharmacokinetic
		parameters, AUC	Nation AUCon a	and C of the
		, -		
		Emtricitabine and p	presented as below.	
		, -		
	,	Emtricitabine and p	presented as below.	
	•	Emtricitabine and p Parameter	resented as below. Ratio	90% CI
	,	Emtricitabine and p Parameter In AUC _{0-tlast}	Ratio 102.2188	90% CI 98.4475- 106.1345
Conclusion:		Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max}	Ratio 102.2188 101.4604 101.4182	90% CI 98.4475- 106.1345 98.1631- 104.8685
Conclusion:		Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confiden	Ratio 102.2188 101.4604 101.4182 ace intervals for	90% CI 98.4475- 106.1345 98.1631- 104.8685 94.9481- 108.3293
Conclusion:		Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confident ratios (Test/Referent	Ratio 102.2188 101.4604 101.4182 ace intervals for the AUC _{0-tl}	90% CI 98.4475- 106.1345 98.1631- 104.8685 94.9481- 108.3293 the log-transformed
Conclusion:	,	Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confident ratios (Test/Referent were within the range)	Ratio 102.2188 101.4604 101.4182 ace intervals for the AUC _{0-tl} ge of 80% to 125 9	90% CI 98.4475- 106.1345 98.1631- 104.8685 94.9481- 108.3293 the log-transformed ast, AUC _{0-∞} and C _{max}
Conclusion:	,	Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confident ratios (Test/Referent were within the range Emtricitabine. The	Ratio 102.2188 101.4604 101.4182 ace intervals for the AUC _{0-th} ge of 80% to 125 9 prefore, the biocomparency of the second secon	90% CI 98.4475- 106.1345 98.1631- 104.8685 94.9481- 108.3293 the log-transformed ast, AUC _{0-∞} and C _{max} % for Tenofovir and
Conclusion:		Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confident ratios (Test/Referent were within the range Emtricitabine. The Product: Single dose	Ratio 102.2188 101.4604 101.4182 10e intervals for the AUC _{0-tl} ge of 80% to 125 9 refore, the bioec	90% CI 98.4475-106.1345 98.1631-104.8685 94.9481-108.3293 the log-transformed ast, AUC _{0-∞} and C _{max} % for Tenofovir and quivalence of Test
Conclusion:		Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confident ratios (Test/Referent were within the range Emtricitabine. The Product: Single dose + Emtricitabine 2	Ratio 102.2188 101.4604 101.4182 ace intervals for ce) for the AUC _{0-fl} ge of 80% to 125 9 refore, the bioeconomic tenorem Tenorem Tablet 00 mg) and Refer	90% CI 98.4475-106.1345 98.1631-104.8685 94.9481-108.3293 the log-transformed ast, AUC _{0-∞} and C _{max} % for Tenofovir and quivalence of Test (Tenofovir 300 mg
Conclusion:		Emtricitabine and p Parameter In AUC _{0-tlast} In AUC _{0-∞} In C _{max} The 90% confident ratios (Test/Referent were within the range Emtricitabine. The Product: Single dose + Emtricitabine 2	Ratio 102.2188 101.4604 101.4182 ace intervals for the AUC _{0-fl} ge of 80% to 125 9 arefore, the bioece TENO-EM Tablet 00 mg) and Referent (Tenofovir 300	90% CI 98.4475-106.1345 98.1631-104.8685 94.9481-108.3293 the log-transformed ast, AUC _{0-∞} and C _{max} % for Tenofovir and quivalence of Test (Tenofovir 300 mg) ence Product: Single