2. STUDY SYNOPSIS

Generic Name:	Lopinavir/Ritonavir
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets
Reference Product:	Aluvia®100/25 mg Tablets
Sponsor's Name:	The Government Pharmaceutical Organization
Study Title:	Comparative Randomized, Single Dose, Two-Way Crossover, Open-Label Study to Determine the Bioequivalence of Lopinavir/Ritonavir Formulations, Lopinavir/Ritonavir 100/25 mg Tablets and Aluvia® 100/25 mg Tablets, after Oral Administration to Healthy Thai Male 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:** Dr. Viravarn Luvira, M.D. Asst. Prof. Vipa Thanachartwet, M.D. Assoc.Prof. Varunee Desakorn Asst.Prof. Jittima Dhitavat **Analytical Investigator:** Dr. Bancha Chuasuwan, B.Sc., Ph.D.(Pharm) **PK & Statistic Investigator**: Ms. Piengthong Narakorn, M.Sc. (Pharmacology)

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Lopinavir/Ritonavir
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets
Reference Product:	Aluvia® 100/25 mg Tablets
Sponsor's Name:	**The Government Pharmaceutical Organization**
IRB/Ethics Approval Date:	Ethics Committee of the Faculty of Tropical Medicine, Mahidol University 420/6 Ratchawithi Rd. Ratchathewi, Bangkok, Thailand 10400. Phone no. +66 2 354 9100-19 # 1535, 1349 Fax no. + 66 2 306 9126 Approval Date: 17 Oct 2013 (for the period from 16 Oct 2013 to 15 Oct 2014)
Objectives:	Primary objective of this study is to assess the rate and extent of absorption of lopinavir/ritonavir from generic lopinavir/ritonavir 100/25 mg tablets manufactured by the Government Pharmaceutical Organization, Thailand and the reference product (Aluvia® product of Abbott GmbH & Co.KG, Germany, each tablet contains lopinavir 100 mg and ritonavir 25 mg) in healthy human male adult subjects, under fasting conditions. Secondary objective of this study is 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.

2. STUDY SYNOPSIS (Cont.)

<table>
<tr><td>Generic Name:</td><td>Lopinavir/Ritonavir</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product:</td><td>Lopinavir/Ritonavir 100/25 mg Tablets</td></tr>
<tr><td>Reference Product:</td><td>Aluvia®100/25 mg Tablets</td></tr>
<tr><td colspan="2">Dosage Regimen:</td><td>Test Product (T):
Lopinavir/Ritonavir 100/25 mg Tablets
Each tablet contains lopinavir 100 mg and ritonavir 25 mg.
Manufactured by The Government Pharmaceutical Organization, Bangkok, Thailand.
Batch No. S550081
Mfg. Date 12 Feb 2012 Exp. Date 12 Feb 2014

Reference Product (R):
Aluvia® 100/25 mg Tablets
Each tablet contains lopinavir 100 mg and ritonavir 25 mg.
Manufactured by Abbott GmbH & Co.KG, Germany
Marketing Authorization Holder: Abbott (Thailand) Ltd, Bangkok.
Batch No. 275298D
Mfg. Date 12 Dec 2012 Exp. Date 30 Nov 2015</td></tr>
<tr><td colspan="2">Clinical Study Site:</td><td>Faculty of Tropical Medicine, Mahidol University
420/6 Ratchawithi road, Ratchathewi, Bangkok, Thailand 10400</td></tr>
</table>

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Lopinavir/Ritonavir
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets
Reference Product:	Aluvia®100/25 mg Tablets
Sponsor's Name:	**The Government Pharmaceutical Organization**
Study Subjects:	50 subjects, selected randomly from healthy adult Thai male volunteers. No. of subjects enrolled: 50 No. of subjects withdrawn / dropped out: 5 No. of subjects completed: 45 No. of subjects analyzed: 50 No. of subjects included in pharmacokinetics and statistical analysis: 45
Demographic Data (N=50):	Age 29.4±6.4 years ; Height 169.9± 6.6 cm; Weight 64.2±8.0 kg ; BMI 22.2±1.8 kg/m^2
Admission and Confinement:	Subjects were housed in the clinical facility for 3 nights, and 4 days in each period (including 2 periods of the study for 6 nights and 8 days). The subjects stayed for one night or at least 10.0 hrs in the facility prior to IMP administration until 48 hrs. after dosing in each period. In case of any adverse event, necessary action would be taken till the event subsides. 50 subjects were housed in the clinical facility for period I but 45 subjects were housed in the clinical facility for period II due to 5 subjects were dropped out.

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Lopinavir/Ritonavir
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets
Reference Product:	Aluvia®100/25 mg Tablets
Sponsor's Name:	**The Government Pharmaceutical Organization**
Drug Administration:	After an overnight fast of at least 10.0 hours, each subject received a single dose of the assigned either Test product-T (Lopinavir/ritonavir 100/25 mg Tablets) or Reference product –R (Aluvia® 100/25 mg Tablets) per their randomization were oral administered with 240 mL of water at ambient temperature by the study personnel.
Study Period:	Screening: 06 Nov 2013 – 15 Nov 2013 Period I: 19 Nov 2013 – 22 Nov 2013 Period II: 25 Nov 2013 – 28 Nov 2013
Washout Period:	6 days washout period between Period-I and Period-II dosing.
Blood Sampling Schedule:	A total of 22 blood samples, each of 05 mL (07 mL in case of pre dose sample) were collected from each subject in each period. Blood samples were drawn at 0.000 (pre-dose) and 0.500, 1.000, 1.500, 2.000, 2.500, 3.000, 3.500, 4.000, 4.500, 5.000, 5.500, 6.000, 6.500, 7.000, 8.000, 9.000, 10.000, 12.000, 16.000, 24.000 and 36.000 hours (post-dose) following drug administration. The total volume of blood draw did not exceed 286±10 mL.

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Lopinavir/Ritonavir	**Sponsor's Name:** **The Government Pharmaceutical Organization**
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets	
Reference Product:	Aluvia®100/25 mg Tablets	
Blood Sampling Handling:		The blood samples for lopinavir/ritonavir were centrifuged at 3000 ± 100 g for 5 minutes below 10°C to separate plasma. The blood samples were kept in ice cool water bath before centrifugation and during separation. The separated plasma were transferred to prelabeled polypropylene tubes in two aliquots [around 1.2 mL in first lot (around 1.5 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. A designated person from bioanalytical facility would receive the samples on arrival. The condition of the samples was examined on arrival and if any of the samples were not in a frozen condition, clinical facility and/or Sponsor would be informed for the same. After receiving the samples at analytical facility, the samples were stored at –65 ± 10°C until completion of analysis.

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<tr><td colspan="2">Analytical Site:</td><td>Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization</td></tr>
<tr><td colspan="2">Bioanalytical Methodology:</td><td>Plasma samples of subjects were assayed for Lopinavir and Ritonavir using a validated LC-MS/MS method.</td></tr>
<tr><td colspan="2">Analyte:</td><td>Plasma Lopinavir and Ritonavir concentration</td></tr>
<tr><td colspan="2">Safety Evaluation:</td><td>Both treatments were well tolerated. No clinically significant or serious ADR were observed</td></tr>
<tr><td colspan="2">Surrogate Parameters:</td><td>Drug plasma concentrations to indicate clinical activity.</td></tr>
<tr><td colspan="2">Primary Pharmacokinetic Parameters:</td><td>The primary pharmacokinetic parameters employed for lopinavir were $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}.
The mean ± SD values of primary pharmacokinetic parameters of lopinavir for Test Product-T and Reference Product-R for forty-five subjects were summarized in the following table :
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<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>$AUC_{0\text{-}tlast}$ (ng.hr/mL)</td><td>4365.053 ± 2846.2154</td><td>4745.798 ± 4311.5164</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng.hr/mL)</td><td>4431.382 ± 2871.5614</td><td>4818.139 ± 4332.2540</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>912.573 ± 422.3789</td><td>916.077 ± 599.3408</td></tr>
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2. STUDY SYNOPSIS (Cont.)

Generic Name:	Lopinavir/Ritonavir	**Sponsor's Name:** **The Government Pharmaceutical Organization**
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets	
Reference Product:	Aluvia®100/25 mg Tablets	
Drug Administration:		After an overnight fast of at least 10.0 hours, each subject received a single dose of the assigned either Test product-T (Lopinavir/ritonavir 100/25 mg Tablets) or Reference product –R (Aluvia® 100/25 mg Tablets) per their randomization were oral administered with 240 mL of water at ambient temperature by the study personnel.
Study Period:		Screening: 06 Nov 2013 – 15 Nov 2013 Period I: 19 Nov 2013 – 22 Nov 2013 Period II: 25 Nov 2013 – 28 Nov 2013
Washout Period:		6 days washout period between Period-I and Period-II dosing.
Blood Sampling Schedule:		A total of 22 blood samples, each of 05 mL (07 mL in case of pre dose sample) were collected from each subject in each period. Blood samples were drawn at 0.000 (pre-dose) and 0.500, 1.000, 1.500, 2.000, 2.500, 3.000, 3.500, 4.000, 4.500, 5.000, 5.500, 6.000, 6.500, 7.000, 8.000, 9.000, 10.000, 12.000, 16.000, 24.000 and 36.000 hours (post-dose) following drug administration. The total volume of blood draw did not exceed 286±10 mL.

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Generic Name:	Lopinavir/Ritonavir
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets
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Sponsor's Name:	**The Government Pharmaceutical Organization**
Blood Sampling Handling:	The blood samples for lopinavir/ritonavir were centrifuged at 3000 ± 100 g for 5 minutes below 10°C to separate plasma. The blood samples were kept in ice cool water bath before centrifugation and during separation. The separated plasma were transferred to prelabeled polypropylene tubes in two aliquots [around 1.2 mL in first lot (around 1.5 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. A designated person from bioanalytical facility would receive the samples on arrival. The condition of the samples was examined on arrival and if any of the samples were not in a frozen condition, clinical facility and/or Sponsor would be informed for the same. After receiving the samples at analytical facility, the samples were stored at –65 ± 10°C until completion of analysis.

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The mean ± SD values of primary pharmacokinetic parameters of lopinavir for Test Product-T and Reference Product-R for forty-five subjects were summarized in the following table :
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2. STUDY SYNOPSIS (Cont.)

Generic Name:	Lopinavir/Ritonavir
Test Product:	Lopinavir/Ritonavir 100/25 mg Tablets
Reference Product:	Aluvia®100/25 mg Tablets

Sponsor's Name:
The Government Pharmaceutical Organization

Primary Pharmacokinetic Parameters:

The primary pharmacokinetic parameters employed for ritonavir were $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}. The mean ± SD values of primary pharmacokinetic parameters of ritonavir for Test Product-T and Reference Product-R for forty-five subjects were summarized in the following table :

Parameters (Units)	(Un-transformed data)	
	Test-T	Reference -R
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	223.270 ± 129.0189	234.238 ± 171.0143
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	234.047 ± 132.8723	246.451 ± 175.4629
C_{max} (ng/mL)	38.661 ± 18.2572	38.615 ± 25.2954

Secondary Pharmacokinetic Parameters:

The secondary pharmacokinetic parameters employed for lopinavir were T_{max}, λ_z, $t_{1/2}$, $AUC_{0\text{-tlast}}$/ $AUC_{0\text{-}\infty}$ and AUC_%Extrap_obs.

Parameters (Units)	(Un-transformed data)	
	Test-T	Reference -R
T_{max} (hr)*	2.000 (0.500, 3.500)	2.000 (1.000, 4.000)
λ_z (1 / hr)	0.399 ± 0.1057	0.378 ± 0.0981
$t_{½}$ (hr)	1.869 ± 0.5209	1.963 ± 0.5403
$AUC_{0\text{-tlast}}$ / $AUC_{0\text{-}\infty}$	0.982 ± 0.0114	0.980 ± 0.0101
AUC_%Extrap_obs (%)	1.823 ± 1.1364	1.979 ± 1.0086

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

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<tr><td>Reference Product:</td><td>Aluvia®100/25 mg Tablets</td></tr>
<tr><td colspan="2">Secondary Pharmacokinetic Parameters:</td><td>The secondary pharmacokinetic parameters employed for ritonavir were T_{max} , λ_z , $t_{1/2}$, $AUC_{0\text{-}tlast}$/ $AUC_{0\text{-}\infty}$ and AUC_%Extrap_obs.
<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>1.500 (0.500, 4.500)</td><td>2.000 (0.500, 4.500)</td></tr>
<tr><td>λ_z (1 / hr)</td><td>0.182 ± 0.0639</td><td>0.174 ± 0.0591</td></tr>
<tr><td>$t_{½}$ (hr)</td><td>4.301 ± 1.5213</td><td>4.579 ± 2.0772</td></tr>
<tr><td>$AUC_{0\text{-}tlast}$ / $AUC_{0\text{-}\infty}$</td><td>0.949 ± 0.0232</td><td>0.941 ± 0.0349</td></tr>
<tr><td>AUC_%Extrap_obs (%)</td><td>5.119 ± 2.3238</td><td>5.928 ± 3.4885</td></tr>
</table>
*T_{max} were represented in median (Min, Max) value</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 Cmax of lopinavir and presented as below.
<table>
<tr><th>Parameters</th><th>Ratios</th><th>90% CI</th></tr>
<tr><td>ln $AUC_{0\text{-}tlast}$</td><td>100.3</td><td>87.42 - 115.16</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>100.2</td><td>87.38 - 114.86</td></tr>
<tr><td>ln C_{max}</td><td>104.2</td><td>92.44 - 117.41</td></tr>
</table></td></tr>
</table>

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<tr><td>Reference Product:</td><td>Aluvia®100/25 mg Tablets</td></tr>
<tr><td colspan="2"></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 ritonavir and presented as below.
<table>
<tr><th>Parameters</th><th>Ratios</th><th>90% CI</th></tr>
<tr><td>ln $AUC_{0\text{-}tlast}$</td><td>101.9</td><td>91.08 - 113.93</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>101.0</td><td>90.64 - 112.44</td></tr>
<tr><td>ln C_{max}</td><td>106.7</td><td>93.81- 121.31</td></tr>
</table></td></tr>
<tr><td colspan="2">Conclusion:</td><td>The Test Product-T (Lopinavir/Ritonavir 100/25 mg Tablets – Manufactured by: GPO, Thailand/ Batch Number – S550081) when compared with the Reference Product-R (Aluvia® 100/25 mg Tablets – Manufactured by: Abbott GmbH & Co.KG, Germany/ Batch No. 275298D) met 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 lopinavir and ritonavir as set in the protocol.</td></tr>
<tr><td colspan="2">Date of Report:</td><td>09 Jun 2014</td></tr>
</table>