2. STUDY SYNOPSIS

Generic Name: Ribavirin 400 mg Tablets **Test Product:** Ribavirin GPO 400 mg Tablets **Reference Product:** Copegus® 400 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 Ribavirin Formulations, Ribavirin GPO 400 mg Tablets and Copegus® 400 mg Tablets, after Oral Administration to Healthy Thai Male Volunteers Under Fed Conditions
Investigators:	Study Director: Dr.Isariya Techatanawat Principal Investigator: Mrs.Piengthong Narakorn Clinical Investigator: Dr.Archawin Rojanawiwat Analytical Investigator: Dr.Bancha Chuasuwan PK & Statistic Investigator: Ms.Busarat Karachot
Project Number:	BE003-14
Protocol Number:	023-12
Ethics Committee Approval Date:	Institute for the Development of Human Research Protections (IHRP) Phone no. +66 2591 3876 +66 2591 3541 Fax no. +66 2591 4125 First date of version and approval date: Version No.: 01 Date: 12 Sep 2012 Approval date: 18 Dec 2012 1st Amendment date of version and approval date: Version No.: 02 Date: 15 Jan 2014 Approval date: 10 Feb 2014

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Ribavirin 400 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Ribavirin GPO 400 mg Tablets	
Reference Product:	Copegus® 400 mg Tablets	
Objectives:		To compare the rate and extent of absorption of ribavirin from ribavirin 400 mg tablets 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: Single dose, Ribavirin GPO 400 mg Tablets Each tablet contains Ribavirin 400 mg Batch No. S550454 Mfg. Date 16 Aug 2012 Exp. Date 16 Aug 2014 Name and address of manufacturer: The Government Pharmaceutical Organization 75/1 Rama VI Road Ratchathewi Bangkok 10400 Thailand Reference Product: Single dose, Copegus® 400 mg Tablets Each tablet contains Ribavirin 400 mg Batch No. N0005 Mfg. Date - Exp. Date Apr 2016 Name and address of manufacturer: Roche Pharma AG, Germany Name and address of importer or authorization holder: The Government Pharmaceutical Organization
Clinical Study Site:		Clinical Research Center, Medical Life Sciences Institute, Department of Medical Sciences, Ministry of Public Health, Tiwanon Rd., Amphur Mueng, Nonthaburi, Thailand 11000

2. STUDY SYNOPSIS (Cont.)

Generic Name: Ribavirin 400 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product: Ribavirin GPO 400 mg Tablets	
Reference Product: Copegus® 400 mg Tablets	
Study Subjects:	44 subjects, selected randomly from healthy adult Thai male volunteers. No. of subjects enrolled: 44 No. of subjects withdrawn/ dropped out: 4 No. of subjects completed: 40 No. of subjects analyzed: 44 No. of subjects included in pharmacokinetics and statistical analysis: 27
Demographic Data of Enrolled Subjects (N=44):	Age = 33.14±8.02 years; Height = 172.16±6.95 cm; Weight= 66.44±7.75 kg, BMI= 22.38±1.84 kg/m^2
Drug Administration:	In each of the 2 study periods, one tablets of test product or one tablets of reference product were orally administered by using with 240±02 mL of water at 30 minutes after the start of the a high fat breakfast (about 800-1,000 cal.). This activity was followed by a mouth check to assess the compliance to dosing.
Demographic Data of Completed Subjects (N=40):	Age = 33.98± 7.85 years, Height = 172.13 ± 7.17 cm, Weight = 66.44 ± 7.69 kg, BMI= 22.39 ± 1.83 kg/m^2
Admission and Confinement:	Subjects were admitted the night before study drug administration, supervised for at least 10 hrs overnight fasting until high fat breakfast menu and then confined until collecting the 24.0 hrs sample. Sample at 48.0 and 72.0 hrs were collected on ambulatory basis in each period.

2. STUDY SYNOPSIS (Cont.)

Generic Name: Ribavirin 400 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product: Ribavirin GPO 400 mg Tablets	
Reference Product: Copegus® 400 mg Tablets	
Study Period:	Screening: 11-13 Feb 2014 and 17-18 Feb 2014 Enrollment: 24 Feb - 11 Apr 2014 Period I: 24 - 28 Feb 2014 Pre check in for safety evaluation: 2 – 3 Apr 2014 Period II: 7 - 11 Apr 2014
Washout Period:	6 weeks
Blood Sampling Schedule:	Twenty-two blood samples (05 mL for post dose and 07 mL for pre-dose sample) were drawn at 0.000 (pre-dose sample) and 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.500, 4.000, 6.000, 8.000, 10.000, 12.000, 24.000, 48.000 and 72.000 hours post dose in vacutainers containing K_2EDTA as an anticoagulant. The total volume of blood draw did not exceed 288 ± 10 mL.
Blood Sampling Handling:	Blood samples which were kept in wet ice bath before centrifugation and during separation were placed in a refrigerated centrifuge within 30 minutes from the time of collection and centrifuged at 3000 ± 100 rcf for 5 minutes below 10°C to separate plasma. Then, they were placed in the freezer or in dry ice box within 60 minutes from the start of centrifugation. The plasma were aliquoted into 2 pre-labeled polypropylene tubes at around 1.0 mL in the first lot (1.5 mL in case of pre dose samples) and rest of the volume in second lot for back up.

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<tr><td>Test Product:</td><td>Ribavirin GPO 400 mg Tablets</td></tr>
<tr><td>Reference Product:</td><td>Copegus® 400 mg Tablets</td></tr>
<tr><td colspan="2">Clinical Sample Storage:</td><td>Bioequivalence Study Group, Research and Development Institute, the Government Pharmaceutical Organization</td></tr>
<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 ribavirin using a validated LC-MS/MS method.</td></tr>
<tr><td colspan="2">Analyte:</td><td>Plasma ribavirin 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 therapeutic effect.</td></tr>
<tr><td colspan="2">Primary Pharmacokinetic Parameters:</td><td>The primary pharmacokinetic parameters employed for ribavirin were AUC_{0-72} and C_{max}.

The mean ± SD values of primary pharmacokinetic parameters of ribavirin for Test Product-T and Reference Product-R for twenty-seven 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>8478.685 ± 3023.6642</td><td>8197.546 ± 2348.0123</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>749.206 ± 295.4677</td><td>743.558 ± 288.7992</td></tr>
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<tr><td>Reference Product:</td><td>Copegus® 400 mg Tablets</td></tr>
<tr><td colspan="2">Secondary Pharmacokinetic Parameters:</td><td>The secondary pharmacokinetic parameters employed for ribavirin were T_{max}.
<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 (0.500,3.500)</td><td>1.250 (0.750,2.750)</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_{0-72} and C_{max} of ribavirin 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>101.3</td><td>95.73-107.17</td></tr>
<tr><td>ln C_{max}</td><td>99.6</td><td>92.50-107.32</td></tr>
</table></td></tr>
<tr><td colspan="2">Conclusion:</td><td>The Test Product-T (Ribavirin GPO 400 mg Tablets – Manufactured by: GPO, Thailand/ Batch Number – S550454) when compared with the Reference Product-R (Copegus® 400 mg Tablets – Manufactured by: Roche Pharma AG, Germany/ Batch No. N0005) met the bioequivalence criteria with respect to the rate and extent of absorption of ribavirin as set in the protocol.</td></tr>
<tr><td colspan="2">Date of Report:</td><td>23 Sep 2014</td></tr>
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