2. STUDY SYNOPSIS

Generic Name: Torsemide 10 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product: Torsemide GPO 10 mg tablets	
Reference Product: Unat® 10 mg tablets	
Study Title:	Comparative Randomized, Single Dose, Two-Way Crossover, Open-Label Study to Determine the Bioequivalence of Torsemide Formulations, Torsemide GPO 10 mg Tablets and Unat® 10 mg Tablets, after Oral Administration to Healthy Thai Volunteers Under Fasting Conditions.
Investigators:	Study Director: Dr.Isariya Techatanawat Principal Investigator: Ms.Piengthong Narakorn Clinical Investigator: Dr.Archawin Rojanawiwat Analytical Investigator: Dr.Bancha Chuasuwan PK & Statistic Investigator: Ms.Piengthong Narakorn
Protocol Number:	008-12
Project Number:	008-12
Ethics Committee Approval Date:	Institute for the Development of Human Research Protections (IHRP) Approval Date 15 Jun 2012 (Protocol Version 01 Version date:11 Jun 2012), Approval date 12 Dec 2012(1st amendment)
Objectives:	To compare the rate and extent of absorption of torsemide from torsemide 10 mg tablets formulation with that of reference formulation. To evaluate the safety and tolerability of the formulations in healthy subjects on the basis of clinical and laboratory examinations at the beginning and at the end of the trial.

2. STUDY SYNOPSIS (Cont.)

Generic Name: Torsemide 10 mg tablets **Test Product:** Torsemide GPO 10 mg tablets **Reference Product:** Unat® 10 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Dosage Regimen:	Test Product: Single dose, 10 mg of Torsemide GPO tablets. Batch No. S540221 Mfg. Date 25 Aug 2011 Exp. Date 25 Aug 2013 Name and address of manufacturer: The Government Pharmaceutical Organization 75/1 Rama VI Road Ratchathewi Bangkok 10400 Thailand Reference Product: Single dose, 10 mg of Unat® tablets. Batch No. E0042B01 Mfg. Date Jan 2010 Exp. Date Jan 2013 Name and address of manufacturer: Roche Farma SA, Spain. Name and address of importer or authorization holder: PL Asia Pacific (Thailand) Ltd., Bangkok
Clinical Study Site:	Clinical Research Center, Department of Medical Sciences, Ministry of Public Health, Thiwanon Rd., Amphur Mueng, Nontaburi, Thailand 11000
Study Subjects:	26 subjects (17 males, 9 females), selected randomly from healthy adult Thai volunteers. No. of subjects enrolled: 26 No. of subjects withdrawn:- No. of subjects completed: 26 No. of subjects analyzed: 26 No. of subjects included in pharmacokinetics and statistical analysis: 26
Demographic Data of Enrolled Subjects (N=26):	Age = 30.31±7.39 years; Height = 170.23±9.04 cm; Weight= 62.89±9.24 kg, BMI= 21.58±1.66 kg/m^2

2. STUDY SYNOPSIS (Cont.)

Generic Name: Torsemide 10 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product: Torsemide GPO 10 mg tablets	
Reference Product: Unat® 10 mg tablets	
Admission and Confinement:	Subjects were admitted the night before study drug administration, supervised for at least 10.0 hrs overnight fasting and then confined until collecting the 24.0 hrs sample in each period.
Drug Administration:	Each subject randomly received a single dose of the assigned formulation, administered with 240 ml of water after an overnight fasting of at least 10.0 hrs.
Study Period:	Screening: 12 - 13 Dec 2012 Enrollment: 18 - 27 Dec 2012 Period I: 18 - 20 Dec 2012 Period II: 25 - 27 Dec 2012
Washout Period:	7 days
Blood Sampling Schedule:	18 blood samples (05 mL for post dose and 07 mL for pre-dose sample) were drawn at 0.000 (pre-dose sample) and 0.167, 0.333, 0.500, 0.667, 0.833, 1.000, 1.250, 1.500, 1.750, 2.000, 3.000, 4.000, 6.000, 8.000, 10.000, 12.000 and 24.000 hrs (post-dose). The total volume of blood drawn did not exceed 212±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 and were placed in the freezer or in dry ice box within 60 minutes from the start of centrifugation. Plasma samples were aliquoted into pre-labelled polypropylene tubes at around 1.7 mL in the first lot (2.2 mL in case of pre dose samples) and rest of the volume in the second lot for back up.

2. STUDY SYNOPSIS (Cont.)

<table>
<tr><td>Generic Name:</td><td>Torsemide 10 mg tablets</td><td rowspan="3">Sponsor's Name:
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<tr><td>Test Product:</td><td>Torsemide GPO 10 mg tablets</td></tr>
<tr><td>Reference Product:</td><td>Unat® 10 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 torsemide using a validated LC MS/MS method.</td></tr>
<tr><td colspan="2">Analyte:</td><td>Torsemide in human plasma</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 torsemide were $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}.
The mean ± SD values of primary pharmacokinetic parameters of torsemide for Test Product-T and Reference Product-R for twenty-six 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>$AUC_{0\text{-}tlast}$ (ng.hr / mL)</td><td>4222.585 ± 747.4567</td><td>4379.601 ± 820.9318</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng.hr / mL)</td><td>4296.891 ± 731.1465</td><td>4453.685 ± 813.2174</td></tr>
<tr><td>C_{max} (ng / mL)</td><td>1802.695 ± 335.6063</td><td>1977.267 ± 390.3282</td></tr>
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2. STUDY SYNOPSIS (Cont.)

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<tr><td>Test Product:</td><td>Torsemide GPO 10 mg tablets</td></tr>
<tr><td>Reference Product:</td><td>Unat® 10 mg tablets</td></tr>
<tr><td colspan="2">Secondary Pharmacokinetic Parameters:</td><td>The secondary pharmacokinetic parameters employed for torsemide 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>0.750 (0.500-2.000)</td><td>0.667 (0.500-1.500)</td></tr>
<tr><td>λ_z (1 / hr)</td><td>0.173 ± 0.0368</td><td>0.170 ± 0.0360</td></tr>
<tr><td>$t_{½}$ (hr)</td><td>4.172 ± 0.7696</td><td>4.231 ± 0.7986</td></tr>
<tr><td>$AUC_{0\text{-tlast}}$ / $AUC_{0\text{-}\infty}$</td><td>0.982 ± 0.0114</td><td>0.983 ± 0.0103</td></tr>
<tr><td>AUC_%Extrap_obs (%)</td><td>1.845 ± 1.1367</td><td>1.749 ± 1.0323</td></tr>
</table>
*T_{max} was represented in median (Min, Max) value.</td></tr>
<tr><td colspan="2">90% Confidence Intervals:</td><td>The 90% confidence intervals were calculated for the ln-transformed primary pharmacokinetic parameters, $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} of torsemide 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>96.5</td><td>93.86-99.29</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>96.6</td><td>93.97-99.37</td></tr>
<tr><td>ln C_{max}</td><td>91.2</td><td>85.64-97.06</td></tr>
</table></td></tr>
</table>

2. STUDY SYNOPSIS (Cont.)

Generic Name:	Torsemide 10 mg tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Torsemide GPO 10 mg tablets	
Reference Product:	Unat® 10 mg tablets	
Conclusion:		The Test Product-T (Torsemide GPO 10 mg tablets – Manufactured by: GPO, Thailand. / Batch Number – S540221) when compared with the Reference Product-R (Unat® 10 mg tablets – Manufactured by: Roche Farma SA, Spain / Batch No. E0042B01) met the bioequivalence criteria of 80.0-125.0% with respect to the rate and extent of absorption.
Date of Report:		23 Aug 2013