2. STUDY SYNOPSIS

<table>
<tr><td>Generic Name: Irbesartan</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product: Irbesartan GPO 150 mg Tablets</td></tr>
<tr><td>Reference Product: Aprovel® 150 mg Tablets</td></tr>
<tr><td>Study Title:</td><td>Comparative Randomized, Single dose, Two-way Crossover, Open-Label Study to Determine the Bioequivalence of Irbesartan Formulation, Irbesartan GPO 150 mg Tablets and Aprovel® 150 mg Tablets, After Oral Administration to Healthy Thai Volunteers Under Fasting Conditions.</td></tr>
<tr><td rowspan="5">Investigators:</td><td>Study Director
Dr. Isariya Techatanawat, B.Sc., Ph.D.</td></tr>
<tr><td>Principal Investigator:
Professor Dr. Punnee Pitisuttithum, M.D., MBBS, D.T.M.&H, FRCPT</td></tr>
<tr><td>Clinical Investigator:
Dr. Viravarn Luvira, M.D.
Asst. Prof. Vipa Thanachartwet, M.D.
Assoc. Prof. Varunee Desakorn
Asst. Prof. Jittima Dhitavat, M.D.</td></tr>
<tr><td>Analytical Investigator:
Dr. Bancha Chuasuwan, B.Sc., Ph.D.(Pharm)</td></tr>
<tr><td>PK & Statistical Investigator:
Ms. Busarat Karachot, , M.Sc. (Pharmacology)</td></tr>
<tr><td>Project Number:</td><td>BE008-14</td></tr>
<tr><td>Protocol Number:</td><td>P009-13</td></tr>
</table>

2. STUDY SYNOPSIS (Continued)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO 150 mg Tablets **Reference Product:** Aprovel® 150 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
IEC/IRB Approval Date:	Ethics Committee of the Faculty of Tropical Medicine, Mahidol University 420/6 Ratchawithi Rd. Ratchathewi, Bangkok, Thailand 10400 Phone no. +66 2 3549100-19 # 1535, 1349 Fax no. + 66 2 3069126 Approval Date: 26 Feb 2014 Protocol version 02, dated 20 Dec 2013 Approval Date: 01 May 2014 Amendment protocol version 03, dated 05 Mar 2014
Objectives:	To compare the rate and extent of absorption of irbesartan from irbesartan 150 mg tablets formulation with that of reference formulation. To evaluate the safety of the formulations in healthy subjects on the basis of clinical and laboratory examinations at the beginning and at the end of the trial.
Dosage Regimen:	**Test Product (T):** Irbesartan GPO 150 mg Tablets Each film coated tablet contains Irbesartan 150 mg. Manufactured by: The Government Pharmaceutical Organization, Bangkok, Thailand. Batch No. S570001 Mfg. Date 06 Jan 2014 Exp. Date 06 Jan 2016

2. STUDY SYNOPSIS (Continued)

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<tr><td>Generic Name: Irbesartan</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product: Irbesartan GPO 150 mg Tablets</td></tr>
<tr><td>Reference Product: Aprovel® 150 mg Tablets</td></tr>
<tr><td>Dosage Regimen (continued):</td><td>Reference Product (R):
Aprovel® 150 mg Tablets
Each film coated tablet contains Irbesartan 150 mg.
Manufactured by: Sanofi Winthrop Industrie, France
Marketing Authorization Holder: Sanofi Aventis, (Thailand) Ltd, Bangkok, Thailand.
Batch No. 3A241
Mfg. Date Jul 2013 Exp. Date Jun 2016</td></tr>
<tr><td>Clinical Study Site:</td><td>Bioequivalence unit, Faculty of Tropical Medicine, Mahidol University
420/6 Ratchawithi road, Ratchathewi, Bangkok, Thailand 10400</td></tr>
<tr><td>Study Subjects:</td><td>28 subjects, selected randomly from healthy adult Thai male volunteers.
No. of subjects enrolled: 28
No. of subjects withdrawn/ dropped out: 0
No. of subjects completed: 28
No. of subjects included in pharmacokinetics: 28
No. of subjects included in statistical analysis: 28</td></tr>
<tr><td>Demographic Data (N=28):</td><td>Age 27.7±7.4 year ; Height 169.3± 5.0 cm;
Weight 63.5±7.2 kg ; BMI 22.1±1.9 kg/m^2</td></tr>
</table>

2. STUDY SYNOPSIS (Continued)

Generic Name:	Irbesartan	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Irbesartan GPO 150 mg Tablets	
Reference Product:	Aprovel® 150 mg Tablets	
Admission and Confinement:		Subjects were housed in the clinical facility for three nights in each period (including 2 periods of the study for six nights). The subjects stayed for one night or at least 10.0 hours in facility prior to IMP administration until 48.0 hours after dosing in each period. Ambulatory samples were performed at 72.00 hours in each study period. In case of any adverse event, necessary action would be taken till event subsides.
Drug Administration:		After an overnight fast of at least 10.0 hours, one tablet of irbesartan 150 mg of test or reference product was administered orally, while in a sitting position, to each subject with 240 mL of drinking water, at ambient temperature by the study personnel.
Study Period:		Screening: 21 Jul 2014 – 24 Jul 2014 Period I: 28 Jul 2014 – 01 Aug 2014 Period II: 04 Aug 2014 – 08 Aug 2014
Washout Period:		07days

2. STUDY SYNOPSIS (Continued)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO 150 mg Tablets **Reference Product:** Aprovel® 150 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Sample collection:	Bedside sampling was collected up to 04 hours post-dose through an indwelling intravenous cannula placed in the forearm vein of the subjects. If required, it may also be collected through a fresh vein puncture. Six (06) mL of blood per sample in each period was withdrawn using syringe and transferred in to pre- labeled vacutainers containing sodium heparin as anticoagulant. Immediately after each tube of blood was drawn, it should be inverted gently several times to ensure the mixing of tube contents (i.e., anticoagulant). Vacutainers were placed upright in a rack kept in wet ice water bath until centrifugation.
Blood Sampling Schedule:	A total of 23 blood samples, each of 06 mL were collected from each subject in each period. The venous blood samples were withdrawn at pre-dose (0.000) and 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 3.000, 3.500, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000, 24.000, 36.000, 48.000 and 72.000 hours following drug administration.

2. STUDY SYNOPSIS (Continued)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO 150 mg Tablets **Reference Product:** Aprovel® 150 mg Tablets	**Sponsor's Name:** The Government Pharmaceutical Organization
Blood Sampling Schedule (continued):	The pre-dose blood sample was collected within a period of 60 minutes before the dosing. Post-dose samples were collected at an interval of ± 02 minutes from the schedule time for all samples. Actual time of sample collection was recorded appropriately. For each subject, combining the two periods, the total volume of blood drawn would be 340±10 mL.
Blood Sampling Handling	Blood samples were placed in a refrigerated centrifuge within 30 minutes from the time of collection and centrifuged. The blood samples were centrifuged at 3000 ± 100 rcf for 5 minutes below 10°C to separate plasma. The blood samples were kept in wet ice water bath before centrifugation and during separation. The separated plasma was transferred to prelabeled polypropylene tubes in two aliquots [(around 1.2 mL in first lot and around 1.0 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.

2. STUDY SYNOPSIS (Continued)

Generic Name: Irbesartan	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product: Irbesartan GPO 150 mg Tablets	
Reference Product: Aprovel® 150 mg Tablets	
Blood Sampling Handling (continued):	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 at -55 ^{o}C or colder. A designated person from bioanalytical facility would receive the samples on arrival. The condition of the samples was examined on arrival. After receiving the samples at analytical facility, the samples were stored at –65 ± 10°C for final storage until completion of analysis.
Clinical Sample Storage:	Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization
Analytical Site:	Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization
Bioanalytical Methodology:	Plasma samples of subjects were assayed for Irbesartan using a validated LC-MS/MS method
Analyte:	Plasma Irbesartan concentration
Safety Evaluation:	Both treatments were well tolerated. No clinically significant or serious ADR were observed
Surrogate Parameters:	Drug plasma concentrations to indicate clinical activity.

2. STUDY SYNOPSIS (Continued)

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<tr><td>Generic Name:</td><td>Irbesartan</td><td rowspan="3">Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Test Product:</td><td>Irbesartan GPO 150 mg Tablets</td></tr>
<tr><td>Reference Product:</td><td>Aprovel®
150 mg Tablets</td></tr>
<tr><td colspan="2">Primary Pharmacokinetic Parameters:</td><td>The primary pharmacokinetic parameters employed for irbesartan were $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}.
The mean ± SD values of primary pharmacokinetic parameters of irbesartan for Test Product-T and Reference Product-R for twenty-eight 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>9507.632 ± 2400.7640</td><td>9003.785 ± 2136.2192</td></tr>
<tr><td>$AUC_{0\text{-}\infty}$ (ng.hr/mL)</td><td>9925.103 ± 2378.8498</td><td>9469.099 ± 2127.9327</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>2373.466 ± 585.3904</td><td>2373.054 ± 584.5355</td></tr>
</table></td></tr>
</table>

2. STUDY SYNOPSIS (Continued)

<table>
<tr><td>Generic Name: Irbesartan
Test Product: Irbesartan GPO 150 mg Tablets
Reference Product: Aprovel® 150 mg Tablets</td><td>Sponsor's Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>Secondary Pharmacokinetic Parameters:</td><td>The secondary pharmacokinetic parameters employed for irbesartan were T_{max}, λ_z, $t_{1/2}$, $AUC_{0\text{-}tlast}$/ $AUC_{0\text{-}\infty}$ and AUC_%Extrap_obs.
The mean ± SD values of secondary pharmacokinetic parameters of irbesartan for Test Product-T and Reference Product-R for twenty-eight 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>T_{max} (hr)*</td><td>1.250 (0.500,5.000)</td><td>1.500 (0.750,3.500)</td></tr>
<tr><td>λ_z (1 / hr)</td><td>0.094 ± 0.0478</td><td>0.089 ± 0.0388</td></tr>
<tr><td>$t_{½}$ (hr)</td><td>9.340 ± 4.9288</td><td>9.753 ± 5.2409</td></tr>
<tr><td>$AUC_{0\text{-}tlast}$ / $AUC_{0\text{-}\infty}$</td><td>0.955 ± 0.0244</td><td>0.949 ± 0.0295</td></tr>
<tr><td>AUC_%Extrap_obs (%)</td><td>4.517 ± 2.4430</td><td>5.142 ± 2.9498</td></tr>
</table>
*T_{max} were represented in median (Min, Max) value.</td></tr>
<tr><td>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 irbesartan (N=28) 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>105.0</td><td>97.89-112.56</td></tr>
<tr><td>ln $AUC_{0\text{-}\infty}$</td><td>104.3</td><td>97.95-110.99</td></tr>
<tr><td>ln C_{max}</td><td>100.0</td><td>92.76-107.77</td></tr>
</table></td></tr>
</table>

2. STUDY SYNOPSIS (Continued)

Generic Name:	Irbesartan	**Sponsor's Name:** The Government Pharmaceutical Organization
Test Product:	Irbesartan GPO 150 mg Tablets	
Reference Product:	Aprovel® 150 mg Tablets	
Conclusion:		The Test Product-T (Irbesartan GPO 150 mg Tablets – Manufactured by: GPO, Thailand/ Batch No. S570001) when compared with the Reference Product-R (Aprovel® 150 mg Tablets – Manufactured by: Sanofi Winthrop Industrie, France/ Batch No. 3A241) meets 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 irbesartan as set in the protocol.
Date of Report:		20 Nov 2014