Protocol No. BEGPO 07/2010

Study No. BEGPO-05/2011

STUDY TITLE: Biocquivalence Study of Irbesartan 300 mg Tablet in Healthy Thai Volunteers

Principal Investigator and Study Director: Dr.Isariya Techatanawat., B.Pharm, Ph.D. Bioequivalence study group, Research and Development Institute, The Government Pharmaceutical Organization. 75/1 Rama VI Rd., Ratchathewi, Bangkok, Thailand 10400 Phone no. +662 2038123 Fax no. +662 3548812	**Sponsor:** The Government Pharmaceutical Organization 75/1 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand
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IRC/EC Approval Date: Institute for Development of Human Research Protection (IHRP) Approval Date 18 May 2011	
Clinical Study Date: 20 June -5 July 2011	
Analytical Study Date: 08 – 16 July 2011	
Approved Signatures: **Principal Investigator:** ..... **Date** 27 / AUG / 2012 **Clinical Investigator:** ..... **Date** 27 / Aug / 2012 **Analytical Investigator:** ..... **Date** 27 / Aug / 12 **PK & Statistics Investigator:** ..... **Date** 27 / AUG / 2012 **Other Investigator:** ..... **Date** 27 / AUG / 2012	

Compliance Statement

Protocol No. BEGPO 07/2010

Study No. BEGPO-05/2011

STUDY TITLE: Bioequivalence Study of Irbesartan 300 mg Tablet In Healthy Thai Volunteers

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, Department of Medical Sciences, Ministry of Public Health and Lambda Therapeutic Research 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		27 / AUG / 2012
Principal Investigator	Signature	Date
Dr.Archawin Rojanawiwat		27 / Aug / 2012
Clinical Investigator	Signature	Date
Mr. Prashant Kale		27 Aug. 12
Analytical Investigator	Signature	Date
Mr. Ronak Patel		27 / AUG / 2012
Statistical Investigator	Signature	Date
Mrs.Achara Eksaengsri		27/ AUG/ 2012
Other Investigator	Signature	Date

Quality Assurance Statement

Protocol No. BEGPO 07/2010

Study No. BEGPO-05/2011

STUDY TITLE: Bioequivalence Study of Irbesartan 300 mg Tablet in Healthy Thai Volunteers

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		27 / 08 / 12
Quality Assurance Team	Signature	Date
Dr.Yaowapa Suvathi		27 / 08 / 12
Head of Quality Assurance Team	Signature	Date

2. SYNOPSIS

Generic Name: Irbesartan **Test Product:** Irbesartan GPO **Reference Product:** Aprovel®	**Sponsor Name:** The Government Pharmaceutical Organization
Study Title:	Bioequivalence Study of Irbesartan 300 mg Tablet in Healthy Thai Volunteers
Investigators:	Principal Investigator and Study Director: Dr.Isariya Techatanawat., B.Pharm, Ph.D. Clinical Investigator: Dr.Archawin Rojanawiwat, M.D.Ph.D. Analytical Investigator: Mr. Prashant Kale, M.Sc. Statistic Investigator: Mr. Ronak Patel, M.Sc Other Investigator: Ms.Achara Eksaengsri, B.Pharm
Protocol Number:	BEGPO 07/2010
Study Number:	BEGPO-05/2011
IRC/Ethics Approval Date:	Institute for Development of Human Research Protection (IHRP) Approval Date 18 May 2011
Objectives:	To compare the rate and extent of absorption of a Irbesartan 300 mg tablet formulation with those of a reference formulation (Aprovel®) 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.

2. SYNOPSIS (Cont.)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO **Reference Product:** Aprovel®	**Sponsor Name:** The Government Pharmaceutical Organization
Dosage Regimen:	**Test Product:** Single dose, 300 mg of Irbesartan GPO Tablet, Batch No.S540008 Mfd. 13 Jan 2011 Exp. 13 Jan 2013
Dosage Regimen:	**Reference Product:** Single dose, 300 mg of Aprovel® Tablet, Batch No.0A022 Mfd. Jun 2010 Exp. Jun 2013
Clinical Site:	Clinical Research Center, Department of Medical Sciences, Ministry of Public Health, 88/7 Tiwanond rd. Nonthaburi 11000, Thailand
Study Subjects:	24 subjects plus 4 alternatives, selected randomly from healthy adult Thai male volunteers No. of subjects enrolled: 28 No. of subjects dropped out/withdrawn: 0 No. of subjects completed: 28 No. of subjects analyzed: 28 No. of subjects included in pharmacokinetics and statistical analysis: 28
Demographic Data of Enrolled and Completed Subject (N = 28):	Total of 28 subjects with average age = 27.43 ± 7.14 years, height = 170.96 ± 5.96 cm, weight = 64.40 ± 8.06 kg, BMI = 21.98 ± 2.05 kg/m^2 and physical examination were indicated that all participants were healthy.
Admission and Confinement:	Subjects were fasted overnight at least 10.0 hrs before dosing and 4.0 hr after dosing. Subjects were discharged after 48.0 hrs after drug administration.

2. SYNOPSIS (Cont.)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO **Reference Product:** Aprovel®	**Sponsor Name:** The Government Pharmaceutical Organization
Drug Administration:	A single dose of Irbesartan 300 mg tablet was administered along with 240 mL of drinking water.
Study Period:	Screening: 24 – 27 May 2011 Enrollment: 20 June – 5 July 2011 Period I: 20 – 28 June 2011 Period II: 27 June – 5 July 2011
Washout Period:	7 Days
Blood Sampling Schedule:	A total of 23 blood samples (6 mL each) were collected at pre-dose (0 hr) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, 72.0 hrs after dosing in each period.
Blood Sampling Handling:	A total of 23 blood samples were collected for 6 mL in Sodium Heparin vacutainers and centrifuged at 5000 ± 100 rpm for 5 minutes below 10 °C. Plasma samples were divided into two aliquots in labeled polypropylene tubes and stored upright in a box containing dry ice or in a freezer at a temperature –65 °C ± 10 °C for interim storage until shipment to Lambda Therapeutic Research Ltd. Thereafter all the received samples were transferred to the freezer maintained at -65 ± 10°C for final storage, to the bioanalytical facility until the completion of analysis. Before analysis, all the samples were verified.
Clinical Sample Storage:	Bioequivalence Study Group, Research and Development Institute, The Government Pharmaceutical Organization

2. SYNOPSIS (Cont.)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO **Reference Product:** Aprovel®	**Sponsor Name:** The Government Pharmaceutical Organization
Analytical Site:	Lambda Therapeutic Research Ltd., Ahmedabad, India.
Bioanalytical Methodology:	Plasma samples of subjects were assayed for Irbesartan using a validated LC-MS / MS method. The LLOQ of method was 50.181 ng / mL.
Analyte:	Irbesartan in human plasma
Safety Evaluation:	A total of 5 adverse events such as dizziness and fainting occurred during the study period. Three subjects who developed dizziness were probable related to test and reference products. The others two subjects who developed fainting were not related to the investigational product. 7 subjects from period I and 7 subjects from period II developed low blood pressure after a administration but none of them developed clinical hypotension during the study period. Clinical laboratory evaluation at the end of study was shown to be safe for all participants.
Surrogate Parameters:	Drug plasma concentrations to indicate clinical activity.

2. SYNOPSIS (Cont.)

Generic Name: Irbesartan **Test Product:** Irbesartan GPO **Reference Product:** Aprovel®	**Sponsor Name:** The Government Pharmaceutical Organization
Primary Pharmacokinetic Parameters:	The primary pharmacokinetic parameter employed for Irbesartan was C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$. The mean ± SD values of primary pharmacokinetic parameters of Irebesartan for Test Product-A and Reference Product-B for twenty seven subjects are summarized in the following table :

Parameters (Units)	(Un-transformed data)	
	Test-A	**Reference -B**
C_{max} (ng / mL)	4093.840 ± 1667.5049	3735.911 ± 1709.7557
$AUC_{0\text{-}tlast}$ (ng.h / mL)	17253.191 ± 7952.7703	15465.457 ± 5476.0329
$AUC_{0\text{-}\infty}$ (ng.h / mL)	18557.131 ± 8185.2863	16667.356 ± 5767.1336

Secondary Pharmacokinetic Parameters:	The secondary pharmacokinetic parameter employed for Irbesartan was T_{max}, λ_z, $t_{½}$ and AUC_%Extrap_obs and Ratio ($AUC_{0\text{-}tlast}$ / $AUC_{0\text{-}\infty}$).

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test-A	**Reference -B**
T_{max} (h)*	1.500 (0.500-5.000)	1.250 (1.1690 – 5.000)
λ_z (1 / h)	0.153 ± 0.1173	0.159 ± 0.1196
$t_{½}$ (h)	8.785 ± 13.8997	7.774 ± 8.8811
AUC_%Extrap_obs (%)	6.813 ± 9.3472	6.969 ± 7.2148
Ratio ($AUC_{0\text{-}tlast}$ / $AUC_{0\text{-}\infty}$)	0.932± 0.0935	0.930 ± 0.0721

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

2. SYNOPSIS (Cont.)

<table>
<tr><td>Generic Name: Irbesartan
Test Product: Irbesartan GPO
Reference Product: Aprovel®</td><td>Sponsor Name:
The Government Pharmaceutical Organization</td></tr>
<tr><td>90% Confidence Intervals</td><td>The 90% parametric confidence intervals were calculated for the ln-transformed primary pharmacokinetic parameters, C_{max}, $AUC_{0-tlast}$ and $AUC_{0-\infty}$ of the Irbesartan and presented as below.
<table>
<tr><th>Parameter</th><th>Ratios</th><th>90% CI</th></tr>
<tr><td>Ln C_{max}</td><td>111.3 %</td><td>100.61-123.19</td></tr>
<tr><td>Ln $AUC_{0-tlast}$</td><td>106.9 %</td><td>99.76-114.53</td></tr>
<tr><td>Ln $AUC_{0-\infty}$</td><td>107.1 %</td><td>98.50-116.47</td></tr>
</table></td></tr>
<tr><td>Conclusion:</td><td>The Test Product-A (Single dose, 300 mg of Irbesartan Tablets–Manufactured By The Government Pharmaceutical Organization 75/1 Rama VI Road, Ratchathewi, Bangkok-10400 Thailand/ Batch No. S540008) when compared with the Reference Product-B [Single dose, 300 mg of Aprovel® Tablets)–Manufactured by: Sanofi Winthorp Industrie, France/Importer : Sanofi Aventis (Thailand), Bangkok, Thailand Batch No. 0A022] meet the bioequivalence criteria with respect to the rate and extent of absorption of Irbesartan as per the criteria set in the Protocol.</td></tr>
<tr><td>Date of Report:</td><td>27 August 2012</td></tr>
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