3. SYNOPSIS

Study Title	Bioequivalence study of two fluconazole capsule formulations in healthy Thai volunteers
Project No.	03004
Investigators	Principal Investigator Wiyada Akarawut, Ph.D. Clinical Investigator Sumana Chompootaweep, M.D. Co-Investigator Triporn Wattananat, Ph.D.
Study Center	Bioequivalence Study Center Bureau of Drug and Narcotic Department of Medical Sciences Tiwanon Road, Nonthaburi 11000, Thailand
Clinical Site	Department of Pharmacology Faculty of Medicine, Chulalongkorn University Rama IV Road, Patumwan, Bangkok 10330, Thailand
Bioanalytical Laboratory	Bioequivalence Study Center Bureau of Drug and Narcotic Department of Medical Sciences Tiwanon Road, Nonthaburi 11000, Thailand
Objective	Evaluation of bioequivalence of two oral capsule formulations of fluconazole 200 mg in healthy Thai volunteers under fasting condition.
Investigational Products	**Test product (T):** Fluzoral capsules containing 200 mg fluconazole. Lot No. S470194 Mfg. Date : 06-10-2004 Expiry Date : 06-10-2007 Mfd. by the Government Pharmaceutical Organization, Thailand **Reference product (R):** Diflucan capsules containing 200 mg fluconazole. Lot No. 114921241 Mfg. Date : 09-2001 Expiry Date : 09-2006 Mfd. by Pfizer Pty, Limited, NSW, Australia
Study Period	**Clinical Phase:** 26 November 2005 - 21 December 2005 **Analytical Phase:** 10-24 January 2006
Study Design	An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose, comparative oral bioavailability study.
Number of Subjects	Total of 20 healthy male subjects were dosed and completed the study.
Dose	Single oral dose of 200 mg x 1 capsule of test (T) or reference (R) product was administered along with 240 mL of water.
Washout Period	Three weeks.

Blood Sampling Schedules	Blood samples were collected in prelabelled tubes containing heparin. The venous blood samples were withdrawn pre-dose, and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 hours post dose.		
Bioanalysis	Fluconazole was measured using a validated HPLC-UV method (LLOQ = 200 ng/mL, calibration curve range = 200–10,000 ng/mL). Phenacetin was used as the internal standard.		
Safety Variables	Safety of subjects was evaluated by general medical examination, checking of clinical laboratory tests, monitoring of vital signs, and documentation of adverse events		
Safety Assessment	No abnormal findings in clinical laboratory tests were reported. No changes in vital signs were reported at screening and during the study. One adverse event in one subject was reported as watery diarrhea which was considered mild. There was no report of serious adverse event or withdrawals because of adverse events.		
Pharmacokinetic Evaluation Criteria	**Pharmacokinetic parameters** - C_{max} was obtained from direct data. - AUC_{0-t} was calculated using the trapezoidal rule. - $AUC_{0-\infty}$ was calculated as sum of AUC_{0-t} and the extrapolated area using the last measured concentration [$C_{(last)}$] and the elimination rate constant. **Bioequivalence** The 90 % confidence intervals were constructed for the ratios of the means of parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test and reference formulations, using Ln-transformed data. Bioequivalence is to be concluded if the confidence intervals fall within 80.0 – 125.0 %.		
Pharmacokinetic Results	**Parameter**	**90 % Confidence Intervals**	**T/R Ratio (%)**
	C_{max}	93.7 – 103.7	98.6
	AUC_{0-t}	96.8 – 106.0	101.3
	$AUC_{0-\infty}$	97.6 – 108.3	102.8
Conclusions	The statistical analysis indicated that pharmacokinetic parameters for Fluzoral (Fluconazole 200 mg) capsules (Test) of the Government Pharmaceutical Organization, Thailand and Diflucan capsules (Reference) of Pfizer, Australia, were within the 80.0 – 125.0 % acceptance range. Therefore Fluzoral (Fluconazole 200 mg) capsules (Test) is bioequivalent to Diflucan capsules (Reference) for both the extent of absorption (AUC) and the rate of absorption (C_{max}). In addition, study treatments were well tolerated, and there were no serious adverse events, and no subject withdrew from the study for safety reasons.		

Figure 1 Linear Plot of Mean Plasma Fluconazole Concentrations Versus Time in Healthy Subjects (N=20)

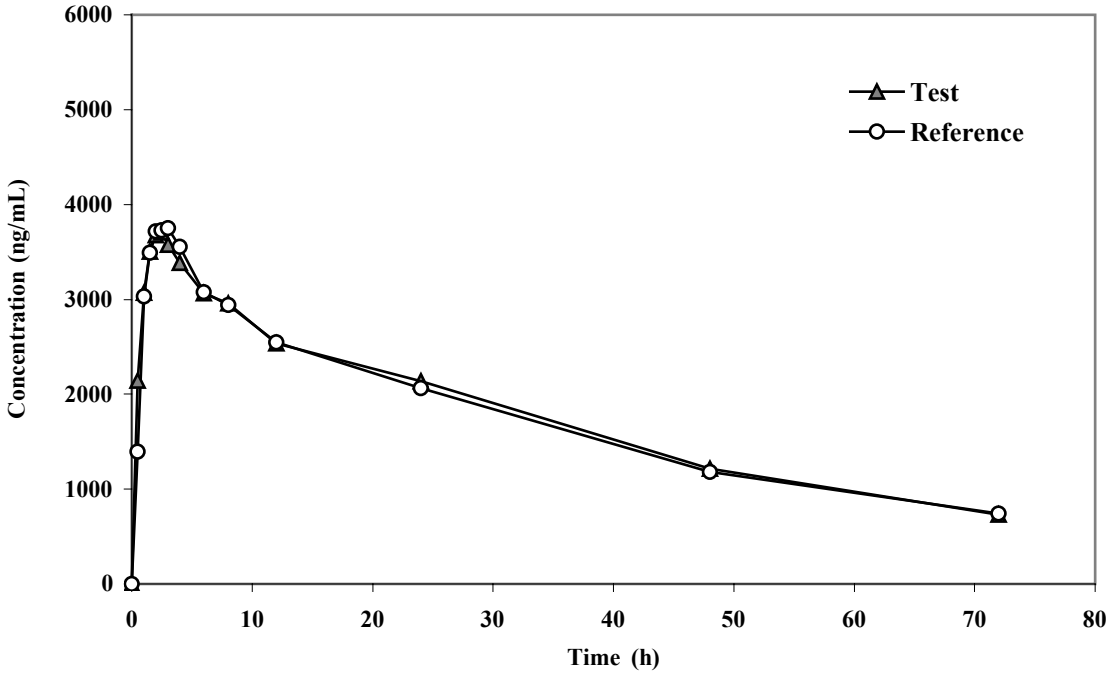

Figure 2 Semi-log Plot of Mean Plasma Fluconazole Concentrations Versus Time in Healthy Subjects (N=20)