3. **SYNOPSIS**

<table>
<thead>
<tr>
<th><strong>Study Title</strong></th>
<th>Bioequivalence study of two fluconazole capsule formulations in healthy Thai volunteers</th>
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<tr>
<td><strong>Project No.</strong></td>
<td>03004</td>
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</table>
| **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

- \( C_{\text{max}} \) was obtained from direct data.
- \( \text{AUC}_{0-t} \) was calculated using the trapezoidal rule.
- \( \text{AUC}_{0-\infty} \) was calculated as sum of \( \text{AUC}_{0-t} \) and the extrapolated area using the last measured concentration \([C_{(\text{last})}]\) and the elimination rate constant.

Bioequivalence

The 90 % confidence intervals were constructed for the ratios of the means of parameters \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) 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

<table>
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<tr>
<th>Parameter</th>
<th>90 % Confidence Intervals</th>
<th>T/R Ratio (%)</th>
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<tbody>
<tr>
<td>( C_{\text{max}} )</td>
<td>93.7 – 103.7</td>
<td>98.6</td>
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<tr>
<td>( \text{AUC}_{0-t} )</td>
<td>96.8 – 106.0</td>
<td>101.3</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} )</td>
<td>97.6 – 108.3</td>
<td>102.8</td>
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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 \( (C_{\text{max}}) \).

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)