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Bioavailability of Single-Dose SUBA-Itraconazole Compared to Conventional Itraconazole under Fasted and Fed Conditions

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ABSTRACT
Conventional itraconazole (C-ITZ) suffers from absorption variability. SUBA-itraconazole (S-ITZ) is more bioavailable than C-ITZ at steady state in a fed condition, but there are no data comparing the two under a fasted state. An open-label, single-dose, randomized, bioequivalence study was performed comparing S-ITZ to C-ITZ capsules under fasted and fed conditions in healthy adults measuring itraconazole and hydroxyitraconazole plasma levels. This study demonstrated less variability of S-ITZ compared to C-ITZ capsules under fasted conditions.

KEYWORDS
itraconazole, endemic mycoses, bioavailability, pharmacokinetics

Itraconazole (ITZ) is a broad-spectrum triazole with antifungal activity against many medically important fungi (1–5). Conventional itraconazole (C-ITZ) is available as a capsule and in oral solution, which have unreliable absorption resulting in variable pharmacokinetics (PK) (5, 6). The effect of food on C-ITZ absorption is subject to interpatient variability up to 15-fold (7). As a result, unpredictable supertherapeutic or subtherapeutic plasma levels of ITZ and its major active metabolite hydroxyitraconazole (OH-ITZ) are occasionally experienced. To overcome these limitations, a novel formulation of ITZ labeled SUper BioAvailable (SUBA)-itraconazole (S-ITZ) was developed. S-ITZ has a relative bioavailability of 180% compared to C-ITZ and an absolute bioavailability up to 90%. The 65-mg capsule S-ITZ formulation achieves bioequivalence to a 100-mg capsule of C-ITZ with fewer adverse events (AEs) (8, 9). There are no data comparing these formulations in fed and fasted states.

This was an open-label, single-dose, randomized, four-period, four-treatment, four-sequence, crossover bioequivalence study evaluating the relative bioavailability of a single oral dose of S-ITZ compared to C-ITZ capsules when administered under fasted and fed conditions. Participants were healthy, aged 18 to 65 years, male or female, nonsmokers, with body mass indices of 18 to 30, and without drug allergies who gave informed consent. Full inclusion and exclusion criteria are listed in Table S1 in the supplemental material. Subjects in a fasted or fed state received S-ITZ 65-mg (10) or C-ITZ 100-mg (11) capsules in each study period (A, B, C, and D) in accordance with the randomization schedule summarized in Table 1. The crossover study design allowed comparison of PK parameters within the same subject. No blinding of doses was performed. Blood samples were collected 60 min prior to dosing and prior to breakfast for subjects following the fed regimen and between 1 and 120 h postdose administration. ITZ and OH-ITZ plasma levels were measured by liquid chromatography with tandem mass spectrometry. The area under the plasma concentration over the dosing interval (AUCt), the area under the plasma concentration extrapolated to infinity (AUCinf), observed maximum plasma concentration (Cmax), the time to Cmax (Tmax), the elimination rate constant (kel), and the half-life (t1/2) were estimated based on plasma measurements.

Descriptive statistics for ITZ and OH-ITZ were performed on plasma concentrations and the estimated PK parameters by treatments. The statistical information provided
for AUC<sub>r</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> were geometric means, arithmetic means, ratios of means, and 90% confidence intervals (CI) with log transformation provided for measures used to demonstrate bioequivalence. Analysis of variance (ANOVA) was performed on log-transformed AUC<sub>r</sub>, AUC<sub>inf</sub>, and C<sub>max</sub>. The absence of food effect was established if the 90% confidence interval of the geometric mean ratio of the fed/fasting state for ITZ AUC<sub>r</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> are contained within the 80 to 125% U.S. Food and Drug Administration (FDA) acceptance limits. The treatment differences in T<sub>max</sub> were analyzed nonparametrically and separately for each pair of contrasts via the Hodges-Lehmann estimator. The point estimate of the Hodges-Lehmann’s median difference and the lower and upper limits of the exact 100\(\times (1 - \alpha)\)% confidence interval for the above median difference were obtained based on the Wilcoxon signed-rank distribution. An asymptotic confidence interval was also computed by applying the normal approximation to the Wilcoxon signed-rank distribution.

Intersubject variability for log-transformed AUC<sub>r</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> was assessed using homogeneity of variance. The variances of the untransformed and log-transformed AUC<sub>r</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> parameters were compared between treatment for study periods A and C (fasted) and between treatment for study periods B and D (fed) graphically using boxplots (see Fig. S1 to S12 in the supplemental material). The differences in variances between log-transformed S-ITZ and C-ITZ were assessed with Bartlett’s or Brown-Forsythe’s test as appropriate. The Statistical Analysis System (SAS v9.2) was used for all statistical computations.

Fifty-two healthy volunteers were initially enrolled. The mean age of the study population analyzed was 39 years (range, 19 to 54 years) composed of 51.9% female and 48.1% males. Most subjects were white (50%), followed by Asian (28.8%) and African-American (21.2%). Fifty volunteers completed the study; two subjects were excluded due to a protocol violation given failure to finish entire high-fat meal and noncompliance with study drug. Subjects with an estimation of the C<sub>max</sub> and AUC in at least one test period were included in analysis. The study medications were well tolerated under fasted and fed conditions (see Tables S2 to S5).

Under the fasted condition, the AUC<sub>inf</sub> and C<sub>max</sub> ITZ levels for S-ITZ were higher than those for C-ITZ (23 and 62%, respectively). Under fed conditions, S-ITZ exhibited a 5% lower AUC<sub>inf</sub> and a 20% lower C<sub>max</sub> compared to C-ITZ. Similar results were observed for OH-ITZ levels and are available in Table 2. There was no T<sub>max</sub> difference between formulations under fasted conditions; under fed conditions, the median T<sub>max</sub> for S-ITZ

### TABLE 1

<table>
<thead>
<tr>
<th>Study period</th>
<th>Treatment received</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>S-ITZ 65 mg x 1 dose under fasted conditions</td>
</tr>
<tr>
<td>B</td>
<td>S-ITZ 65 mg x 1 dose under fed conditions</td>
</tr>
<tr>
<td>C</td>
<td>C-ITZ 100 mg x 1 dose under fasted conditions</td>
</tr>
<tr>
<td>D</td>
<td>C-ITZ 100 mg x 1 dose under fed conditions</td>
</tr>
</tbody>
</table>

*a* S-ITZ, SUBA-itraconazole; C-ITZ, conventional itraconazole. Subjects under fasted conditions (A and C) received their dose following an overnight fast of at least 10 h; subjects under fed conditions (B and D) received their dose within 30 min of consuming a high-fat, high-calorie meal (total protein calories, 150; carbohydrate calories, 250; and fat calories, 500), preceded by an overnight fast of at least 10 h. After dosing, all subjects fasted for at least 4 h in all periods. The interval between doses in each study period was at least 14 days. Subjects swallowed one whole capsule with 240 ml of ambient temperature water, and any other fluids (except for milk given with the meal) were restricted from 1 h predosing until 1 h postdose. Caffeine-containing foods and beverages were not allowed within 72 h prior to the dose in each period and throughout the times of blood sample collection. Grapefruit was not allowed for 7 days prior to the first dosing occasion and until after completion of the study.
**TABLE 2** Pharmacokinetic results of itraconazole and hydroxyitraconazole levels comparing SUBA-itraconazole and conventional itraconazole under fasted and fed states

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Itraconazole</th>
<th>Hydroxyitraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-ITZ: fasted (65 mg ITZ)</td>
<td>S-ITZ: fasted (65 mg ITZ)</td>
</tr>
<tr>
<td></td>
<td>C-ITZ: fasted (100 mg ITZ)</td>
<td>C-ITZ: fasted (100 mg ITZ)</td>
</tr>
<tr>
<td>Median $T_{\text{max}}$ in h (range)</td>
<td>2.50 (1.50–5.00)</td>
<td>7.50 (4.50–24)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>111.910 (44)</td>
<td>50.299 (50)</td>
</tr>
<tr>
<td>AUC$_{\text{inf}}$ (ng·h/ml)</td>
<td>1,006.534 (45)</td>
<td>684.773 (46)</td>
</tr>
<tr>
<td>$T_{\text{half}}$ (h)</td>
<td>31.45 (23)</td>
<td>32.48 (26)</td>
</tr>
</tbody>
</table>

*S-ITZ, SUBA-itraconazole; C-ITZ, conventional itraconazole; ITZ, itraconazole; $C_{\text{max}}$, maximum concentration; AUC$_{\text{inf}}$, area under the plasma concentration over the dosing interval; AUC$_{\text{t}}$, area under the curve extrapolated to infinity; $k_{\text{el}}$, elimination rate constant; $T_{\text{half}}$, half-life. $C_{\text{max}}$, AUC$_{\text{t}}$, AUC$_{\text{inf}}$, $k_{\text{el}}$, and $T_{\text{half}}$ are expressed as the arithmetic mean (CV%).

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The geometric mean S-ITZ/C-ITZ ratios for ITZ levels under fasted conditions were 122.76% (90% CI = 109.72 to 137.34%) and 161.75% (90% CI = 141.40 to 185.02%) for AUC\textsubscript{inf} and \( C_{\text{max}} \), respectively (Table 3). Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios for ITZ were 94.67% (90% CI = 85.35 to 105.01%) and 80.26% (90% CI = 67.61 to 95.27%) for the AUC\textsubscript{inf} and \( C_{\text{max}} \), respectively (Table 3). The geometric mean S-ITZ/C-ITZ ratios for OH-ITZ under fasted conditions were 125.77% (90% CI = 111.40 to 141.99%) and 143.40% (90% CI = 128.19 to 160.42%) for the AUC\textsubscript{inf} and \( C_{\text{max}} \), respectively. Under fed conditions, the geometric mean S-ITZ/C-ITZ ratios were 91.86% (90% CI = 79.26 to 106.47%) and 84.25% (90% CI = 73.09 to 97.11%) for the AUC\textsubscript{inf} and \( C_{\text{max}} \), respectively (Table 3).

Decreased relative bioavailability in the presence of food was seen for S-ITZ and C-ITZ. The mean AUC\textsubscript{inf} and \( C_{\text{max}} \) for both ITZ and OH-ITZ were lower (31 and 40% for AUC\textsubscript{inf}; 57 and 54% for \( C_{\text{max}} \)) when S-ITZ was administered after the study meal; a similar decrease was seen in C-ITZ (10 and 18% for AUC\textsubscript{inf}; 14 and 22% for \( C_{\text{max}} \)) for ITZ and OH-ITZ, respectively (Table 3).

Regarding intersubject variability, treatment C (C-ITZ under fasting conditions) for both AUC and \( C_{\text{max}} \) ITZ parameters, exhibited the largest variability (0.422 and 0.372 variances, respectively). While treatment for study period B (S-ITZ under fed conditions) exhibited the lowest intersubject (0.179 and 0.187, respectively). These observed differences did not reach statistical significance. Similarly, the largest intersubject variability of OH-ITZ was exhibited by treatment for study period C for AUC\textsubscript{n} and \( C_{\text{max}} \) (0.456, 0.439, and 0.246, respectively). The lowest values for the intersubject variance within each parameter were exhibited by treatment B: 0.214, 0.218, and 0.129, respectively. The only parameter that reached statistical significance (\( P = 0.0028 \)) under fasting conditions was the difference between the variability of the \( C_{\text{max}} \).

This study adds to the growing body of evidence that S-ITZ achieves bioequivalence to C-ITZ in terms of the extent of exposure for both ITZ and OH-ITZ, as measured by AUC\textsubscript{n} and AUC\textsubscript{inf} (12–14). In the fasting state, S-ITZ exhibited 23% larger AUC\textsubscript{n} and AUC\textsubscript{inf} values with geometric means within the wider bioequivalence range. In the fed state compared to C-ITZ capsules, S-ITZ had a 10% lower AUC\textsubscript{n} and a 5% lower AUC\textsubscript{inf}, which is within the wider bioequivalence range as defined by the FDA (15). This continued affirmation of the bioequivalence of clinically important PK parameters between S-ITZ and C-ITZ allows clinicians to optimize therapeutic choice based upon more patient-centered parameters—less restrictive administration conditions, lower interpatient variability, and subjective drug tolerability.

In this study, administration in a fed state decreased bioavailability of C-ITZ capsule formulation. This runs counter to historical literature of improved bioavailability in the

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Contrast in ( C_{\text{max}} ) (ng/ml)</th>
<th>Contrast in AUC\textsubscript{inf} (ng \cdot h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RGM (%)</td>
<td>90% CI</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-ITZ fasted vs C-ITZ fasted</td>
<td>161.75</td>
<td>141.40–185.02</td>
</tr>
<tr>
<td>S-ITZ fed vs C-ITZ fed</td>
<td>80.26</td>
<td>67.61–95.27</td>
</tr>
<tr>
<td>S-ITZ fed vs S-ITZ fasted</td>
<td>42.87</td>
<td>36.61–50.20</td>
</tr>
<tr>
<td>C-ITZ fed vs C-ITZ fasted</td>
<td>86.40</td>
<td>74.38–100.37</td>
</tr>
<tr>
<td>S-ITZ fasted vs C-ITZ fed</td>
<td>187.20</td>
<td>164.23–213.40</td>
</tr>
<tr>
<td>Hydroxyitraconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-ITZ fasted vs C-ITZ fasted</td>
<td>143.40</td>
<td>128.19–160.42</td>
</tr>
<tr>
<td>S-ITZ fed vs C-ITZ fed</td>
<td>84.25</td>
<td>73.09–97.11</td>
</tr>
<tr>
<td>S-ITZ fed vs S-ITZ fasted</td>
<td>45.66</td>
<td>40.06–52.04</td>
</tr>
<tr>
<td>C-ITZ fed vs C-ITZ fasted</td>
<td>77.72</td>
<td>68.60–88.05</td>
</tr>
<tr>
<td>S-ITZ fasted vs C-ITZ fed</td>
<td>184.51</td>
<td>166.39–204.60</td>
</tr>
</tbody>
</table>

\( S\)-ITZ, SUBA-itraconazole; C-ITZ, conventional itraconazole; \( C_{\text{max}} \), maximum concentration; CI, confidence interval; RGM, ratio of geometric means; IS CV, intrasubject coefficient of variation; AUC\textsubscript{inf}, area under the curve extrapolated to infinity.
fed state compared to a fasted state (7, 16–19), though it is consistent with more recent data (12, 13). We posit this discrepancy reflects the difficulty clinicians have understanding the complicated PK of C-ITZ. Although supertherapeutic levels have increased adverse events, subtherapeutic levels are associated with poor clinical outcomes (20, 23, 25, 26). To ameliorate the issues with capsule administration, a C-ITZ oral solution was developed, although many patients do not tolerate it due to the unpalatable taste and poor gastrointestinal tolerability (21, 22).

More recently, S-ITZ was designed to improve bioavailability and received FDA approval in 2018 (10). The success of this development goal is evidenced by plasma trough levels minimally affected by fasted or fed conditions and enhanced absorption in the presence of acid suppression (13). Prior data comparing S-ITZ to C-ITZ capsule formulation demonstrated the relative bioavailability of S-ITZ was 173%, with 21% less interpatient variability (12). Our study had similar findings of greater bioavailability of S-ITZ compared to C-ITZ given the bioequivalence at a lower dose of 65 mg versus 100 mg. The interpatient variability in our study was lower in the S-ITZ than the C-ITZ, although it did not reach statistical significance but continued to demonstrate a trend of decreased intersubject variability (12, 14). An additional study identified a trend toward treatment failure in the C-ITZ solution group; S-ITZ had 7.4% treatment failure compared to 23.3% for the C-ITZ solution, though it did not reach statistical significance ($P = 0.096$) (23).

S-ITZ has performed favorably throughout early trials and recent direct comparison studies to other ITZ formulations. The growing body of literature on the PK of S-ITZ suggest improved relative bioavailability and less restrictive administration conditions (12, 13, 18). The lone comparison trial in an at-risk patient population showed faster time to therapeutic levels and fewer patients with subtherapeutic levels (23). Promising data continue to accumulate while awaiting the results of MSG15, a trial comparing S-ITZ to C-ITZ for the treatment of endemic mycoses (23).

**SUPPLEMENTAL MATERIAL**

Supplemental material is available online only.

**SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.**

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