Pharmacokinetic Analysis of SUBA™-itraconazole Capsules Compared to Conventional Itraconazole Capsules for a 3-Day Loading Dose Regimen and after 15 Days of Administration

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Background

Itraconazole is a broad-spectrum antifungal agent for the treatment of systemic fungal infections. Conventional forms of itraconazole (CI) capsules are known to have reduced bioavailability with acid suppression and food effects as well as intra- and inter-subject variability.[1-3]

SUBA®-itraconazole (SI), a new form of itraconazole dispersed in a polymer matrix which releases drug in the duodenum rather than the stomach, was recently approved for treatment of systemic mycoses in the US.[4] Plasma trough levels are unaffected whether taken fasted or fed and there is enhanced absorption in the presence of acid suppression.[5]

Two pharmacokinetic studies, a 3-day loading regimen and a 15-day steady-state analysis, were performed comparing 65 mg SI capsules to 100 mg CI capsules to investigate their bioequivalence in support of FDA approval.

Materials and Methods

Both trials were open-label, randomized, two-treatment, two-sequence, two-period, crossover, multiple-dose, oral bioequivalence studies under fed conditions in healthy adults. In the first study, 15 subjects were administered SI (2x65mg) and CI (2x100mg) TID for 3 days and once on day 4. Blood samples were collected on days 1-4 prior to administration and over 8 hours after the last dose on day 4.

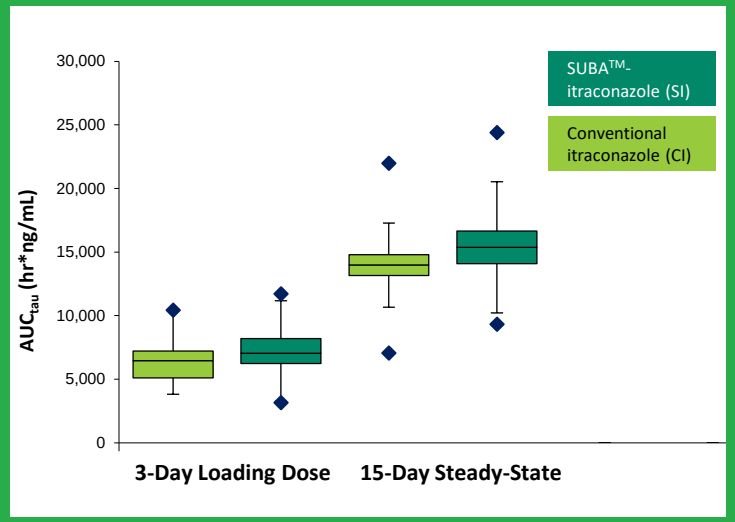
In the second study, 16 subjects were administered SI (2x65mg) and CI (2x100mg) BID for 14 days and a last dose 30min after a meal on day 15. Blood samples were collected on days 1, 13, 14, and 15 prior to administration and from 0.5 to 12 hours after the last dose on day 15. Analysis was by least-squares-geometric means of $C_{max,ss}$, C_{trough} and AUC_{tau}.

Results

For the 3-day loading dose study, the mean age of the study population analyzed (n = 15) was 41±11 yrs composed of 8 female/7 male, 12 black, 2 white and 1 Asian. Sixteen (16) subjects were analyzed for safety having received SI. One (1) subject did not accrue data in both the SI and CI phases.

For the 15-day steady-state study, the mean age of the study population analyzed (n = 16) was 33±9 yrs composed of 7 female/9 male, 12 black, 2 multi-racial, 1 white and 1 American Indian/Alaska native. Twenty-four (24) subjects were initially enrolled. Twenty (20) subjects were analyzed for safety having received SI. Eight (8) subjects discontinued participation from the study prior to PK sampling (Day 15) in Period 2.

Results Continued



3-Day Loading Dose Study (n = 15 Analyzed) Plasma Itraconazole				
	SUBA®-itraconazole (SI)	Conventional itraconazole (CI)		
Parameter	Geometric Mean	Geometric Mean	SI/CI Ratio (%)	90% Confidence Interval
$C_{max,ss}$ (ng/mL)	1,055.3	921.3	114.54	103.40-126.88
C_{trough} (ng/mL)	881.1	820.6	107.37	95.58-120.62
AUC_{tau} (hr*ng/mL)	6,881.7	6,236.2	110.35	100.10-121.66
15-Day Steady-State Study (n = 16 Analyzed) Plasma Itraconazole				
$C_{max,ss}$ (ng/mL)	1,632.2	1,457.5	111.99	104.87-119.59
C_{trough} (ng/mL)	1,187.4	1,004.9	118.16	110.20-126.69
AUC_{tau} (hr*ng/mL)	15,562.1	14,065.1	110.64	104.01-117.70

In both the loading dose and steady-state studies, $C_{max,ss}$, C_{trough} and AUC_{tau} of plasma itraconazole for SI were consistently higher compared to CI (Table). The 90% confidence intervals of the relative mean plasma itraconazole levels of $C_{max,ss}$ and AUC_{tau} for SI, however, were between 80 and 125% demonstrating bioequivalence to CI. Hydroxyitraconazole levels followed the same trends in both studies. From patient level data, 81% (13 of 16) of SI compared to 44% of CI subjects achieved a C_{trough} level of 1034ng/mL at steady-state, the average C_{trough} value for the CI group. When the C_{trough} was corrected for dosage of each formulation [1.18(100mg/65mg)], the relative bioavailability of the SI was 1.82 compared to CI. Both drugs were well-tolerated in both studies. All TEAEs resolved at the end of the studies. One CI subject discontinued due to an AE in the steady-state study. No SAEs were reported.

Conclusion

Total and peak itraconazole exposure was relatively similar between treatments, but SUBA®-itraconazole 65 mg capsules achieved almost 2x greater relative bioavailability than 100 mg conventional itraconazole capsules with a similar safety profile. This new, more bioavailable formulation may offer a benefit in the treatment of systemic mycoses by maintaining blood levels of itraconazole in patients.

References

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