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A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Oral Doses of VT-1161 in Healthy Japanese and Western Subjects

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Introduction

- VT-1161 is a novel, selective inhibitor of fungal CYP51 under development for the treatment of onychomycosis and recurrent vulvovaginal candidiasis.
- VT-1161 has been safe and well tolerated in four Phase 1 studies, two Phase 2a studies, and two Phase 2b studies.

Objectives

- To determine the safety, tolerability and PK profile of multiple oral doses of VT-1161 in healthy Japanese and Western subjects.

Methods

Study Design

- This was a Phase 1, open-label study in healthy adult Japanese and Western subjects conducted at a single center in the United States (Table 1). Subjects were administered either 300 or 600 mg of VT-1161 *qd* on Days 1 through 14, thirty minutes after the start of a moderate-fat, moderate-calorie breakfast.

Table 1: Study Design

Cohort	N (Planned)	Subject Group	Treatment
1	12	Japanese	300 mg VT-1161 *qd* X 14 days
2	12	Western	300 mg VT-1161 *qd* X 14 days
3	12	Japanese	600 mg VT-1161 *qd* X 14 days
4	12	Western	600 mg VT-1161 *qd* X 14 days

Methods (Continued)

Study Population

- Healthy males and females ages 18-65 years, with BMI 18-32 kg/m^2.
- Japanese subjects must have been born in Japan with both biological parents and four biological grandparents of Japanese descent and lived outside of Japan for less than 10 years.
- Western subjects must have had both biological parents and four biological grandparents of non-Asian descent.

Safety Assessments

- Safety was assessed by collection of TEAEs, vital signs, ECGs, and clinical labs. The Safety Population consisted of all subjects who received at least one dose of IMP and had at least one valid post-baseline safety evaluation (51 subjects).

PK Assessments

- Sparse samples were collected throughout the dosing period and serial samples were collected from pre-Day 14 dose to 72 hours post-Day 14 dose. C_{max} and AUC_{72} estimates were calculated from the Day 14 dose.
- Distal toenail clippings were collected on Day 28 for analysis of VT-1161 toenail concentrations.

Results

- 51 subjects were enrolled and 45 completed the study.
  - Four Japanese subjects did not complete the study: two withdrew voluntarily, one due to protocol violation (positive drug screen), and one due to an AE (rash) deemed unlikely-related.
  - Two Western subjects did not complete the study: one due to protocol violation (subject declined to eat pre-dose breakfast) and one by physician decision (subject cited transportation concerns).

Results (Continued)

Table 2: Demographics of Safety Population

Characteristic	300 mg *qd* X 14 Days		600 mg *qd* X 14 Days	
	Cohort 1 Japanese (n = 13)	Cohort 2 Western (n = 14)	Cohort 3 Japanese (n = 12)	Cohort 4 Western (n = 12)
Age, mean (range), years	32.3 (22-46)	37.5 (19-55)	38.8 (21-52)	37.6 (23-52)
Weight, mean (SD), kg	60.3 (10.28)	76.5 (11.06)	67.3 (12.95)	71.3 (12.30)
BMI, mean (SD), kg/m^2	22.6 (2.57)	26.2 (2.44)	24.0 (2.89)	24.2 (2.50)
Female Male	7 (54%) 6 (46%)	7 (50%) 7 (50%)	7 (58%) 5 (42%)	5 (42%) 7 (58%)
Asian Caucasian African-American	13 (100%) 0 (0%) 0 (0%)	0 (0%) 7 (50%) 7 (50%)	12 (100%) 0 (0%) 0 (0%)	0 (0%) 5 (42%) 7 (58%)

- In the 300 mg dose groups (Cohorts 1 and 2), baseline weight and BMI were notably higher in Western subjects. All demographics were similar in the 600 mg dose groups.

Safety Endpoints

- Overall, VT-1161 was safe and well tolerated. There were no SAEs reported. 35 TEAEs were reported by 17/51 (33%) subjects (8 Japanese subjects and 9 Western subjects). All TEAEs were mild or moderate in severity and none were considered by the Investigator to be related to IMP.

PK Endpoints

- At 300 mg, C_{max} and AUC_{72} were approximately 40% higher in Japanese subjects, likely due to the differences in weight and/or BMI between Cohorts 1 and 2. At 600 mg, C_{max} and AUC_{72} were approximately 10% higher in Japanese subjects; the weight and BMI differences between Cohorts 3 and 4 were minimal (Table 3 and Figure 1).
- VT-1161 toenail concentrations on Day 28 increased in a dose-proportional manner and were similar between Japanese and Western subjects.

Figure 1: Mean Plasma VT-1161 Concentration-Time Profiles

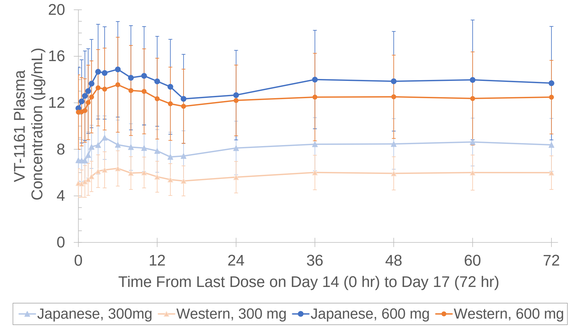

Table 3: Day 14 Plasma VT-1161 PK Parameters and Day 28 Toenail VT-1161 Concentrations

Parameter	300 mg *qd* X 14 Days		600 mg *qd* X14 Days	
	Cohort 1 Japanese (n = 11)	Cohort 2 Western (n = 12)	Cohort 3 Japanese (n = 11)	Cohort 4 Western (n = 12)
C_{max}, mean (SD), µg/mL	9.4 (2.1)	6.6 (1.5)	15.6 (4.2)	14.1 (4.2)
Japanese:Western Ratio	1.42		1.10	
AUC_{72}, mean (SD), µg*hr/mL	595 (153)	421 (101)	982 (307)	894 (250)
Japanese:Western Ratio	1.41		1.10	
Toenail Conc. (SD), ng/g nail	436 (137)	370 (310)	754 (708)	692 (567)
Japanese:Western Ratio	1.18		1.09	

Conclusions

- VT-1161 was safe and well-tolerated in both Japanese and Western subjects.
- VT-1161 plasma exposure was higher in Japanese subjects than Western subjects in both the 300 and 600 mg dose groups, though differences were less pronounced in the 600 mg dose group. The difference in VT-1161 plasma exposure was likely due to differences in subject weight and/or BMI.