Poster #7516

A Phase 1 Multiple Ascending-Dose Trial of VT-1161, a Highly Potent and Selective Oral Antifungal Agent for the Treatment of Superficial Fungal Infections

RJ Schotzinger[1], TP Degenhardt[1], WA Wargin[2], JG Still[3], MJ Guitierrez[4], WR Moore[1], MS Rudoltz[5]

[1]Viamet Pharmaceuticals, Durham, NC; [2]Kinetigen, Durham, NC; [3]Aptiv Solutions, Durham, NC; [4]Comprehensive Phase 1, Miramar, FL, [5]MSR Healthcare Consultants, West Orange, NJ

This study was sponsored by Viamet Pharmaceuticals

Summer Meeting of the American Academy of Dermatology, July 31 - August 4, 2013, New York, NY

VT-1161 Background

- The use of oral terbinafine and azoles for onychomycosis is limited by poor therapeutic profiles:
  - Suboptimal efficacy
  - Drug interactions
  - Hepatic toxicity
- Oral VT-1161, an inhibitor of fungal CYP51, was rationally-designed to avoid the liabilities of current antifungal agents
  - Highly selective and potent against desired fungal target
  - Broad antifungal spectrum
  - Very well tolerated in preclinical safety testing
  - Robust results in preclinical dermatophyte models

VT-1161 Background (cont.)

- Oral VT-1161 was safe and well tolerated in a single ascending-dose Phase 1 study in human volunteers
  - No evidence of drug-related safety issues
  - No evidence of drug-related laboratory issues
  - Excellent oral pharmacokinetic profile with long half-life

Approach: VT-1161 Phase 1 MAD Design

- “A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Oral Doses of VT-1161 in Healthy Adult Subjects”
- Dosing: 40 mg, 80 mg, 160 mg, or 320 mg daily x 7 days with food
- Number of Subjects: 32
  - 24 active (6 per cohort)
  - 8 placebo (2 per cohort)
- Safety assessed by adverse event reporting, physical examination, vital signs, ECGs and laboratory assessments
- Drug levels assessed in plasma, skin and nails

VT-1161 MAD Results: Demographics

Patient Demographics for Multiple-Dose Phase 1 Cohorts					
	Dose Group				
	Placebo	40 mg	80 mg	160 mg	320 mg
Age (years) (SD)	30.3 (8.0)	47.5 (4.9)	38.5 (9.7)	43.7 (5.6)	43.7 (9.8)
Gender Female Male	 2 (25%) 6 (75%)	 3 (50%) 3 (50%)	 3 (50%) 3 (50%)	 0 (0%) 6 (100%)	 1 (16.7%) 5 (83.3%)
Race African American White	 2 (25%) 6 (75%)	 1 (16.7%) 5 (83.3%)	 0 (0%) 6 (100%)	 2 (33.3%) 4 (66.7%)	 1 (16.7%) 5 (83.3%)
Ethnicity Hispanic/Latino Not Hispanic/Latino	 8 (100%) 0 (0%)	 6 (100%) 0 (0%)	 6 (100%) 0 (0%)	 3 (50%) 3 (50%)	 4 (66.6%) 2 (33.3%)
Height (cm) (SD)	167.66 (5.7)	165.80 (6.2)	165.13 (10.5)	172.55 (6.4)	172.68 (13.5)
Weight (kg) (SD)	76.73 (9.5)	77.50 (6.8)	76.57 (10.4)	85.83 (6.7)	84.65 (15.5)
BMI (kg/m^2) (SD)	27.20 (1.9)	28.17 (1.1)	28.20 (3.7)	28.85 (1.9)	28.25 (2.8)

VT-1161 MAD Results: Adverse Events

Adverse Events in Multiple-Dose Phase 1 by Dose Cohort

	Dose Group				
	Placebo	40 mg	80 mg	160 mg	320 mg
Number of subjects with at least 1 AE	1 (12.5%)	4 (66.7%)	4 (66.7%)	1 (16.7%)	1 (16.7%)
Eye Disorders					
Ocular hyperaemia	0	1 (16.7%)	0	0	0
GI Disorders					
Constipation	0	0	2 (33.3%)	0	0
Toothache	0	1 (16.7%)	0	0	0
General Disorders					
Influenza-like illness	0	0	1 (16.7%)	0	0
Injury, Poisoning and Procedural Complications					
Laceration	0	1 (16.7%)	0	0	0
Nervous System Disorders					
Headache	1 (12.5%)	1 (16.7%)	0	0	1 (16.7%)

VT-1161 MAD Results: Adverse Events (cont.)

Adverse Events in Multiple Dose Phase 1 by Dose-Cohort (cont.)

	Dose Group				
	Placebo	40 mg	80 mg	160 mg	320 mg
Reproductive System and Breast Disorders					
Vaginal discharge	0	0	1 (16.7%)	0	0
Respiratory, Thoracic and Mediastinal Disorders					
Oropharyngeal pain	0	1 (16.7%)	0	0	0
Skin and Subcutaneous Tissue Disorders					
Rash	0	0	1 (16.7%)	1 (16.7%)	0

VT-1161 MAD Results: Liver Enzymes

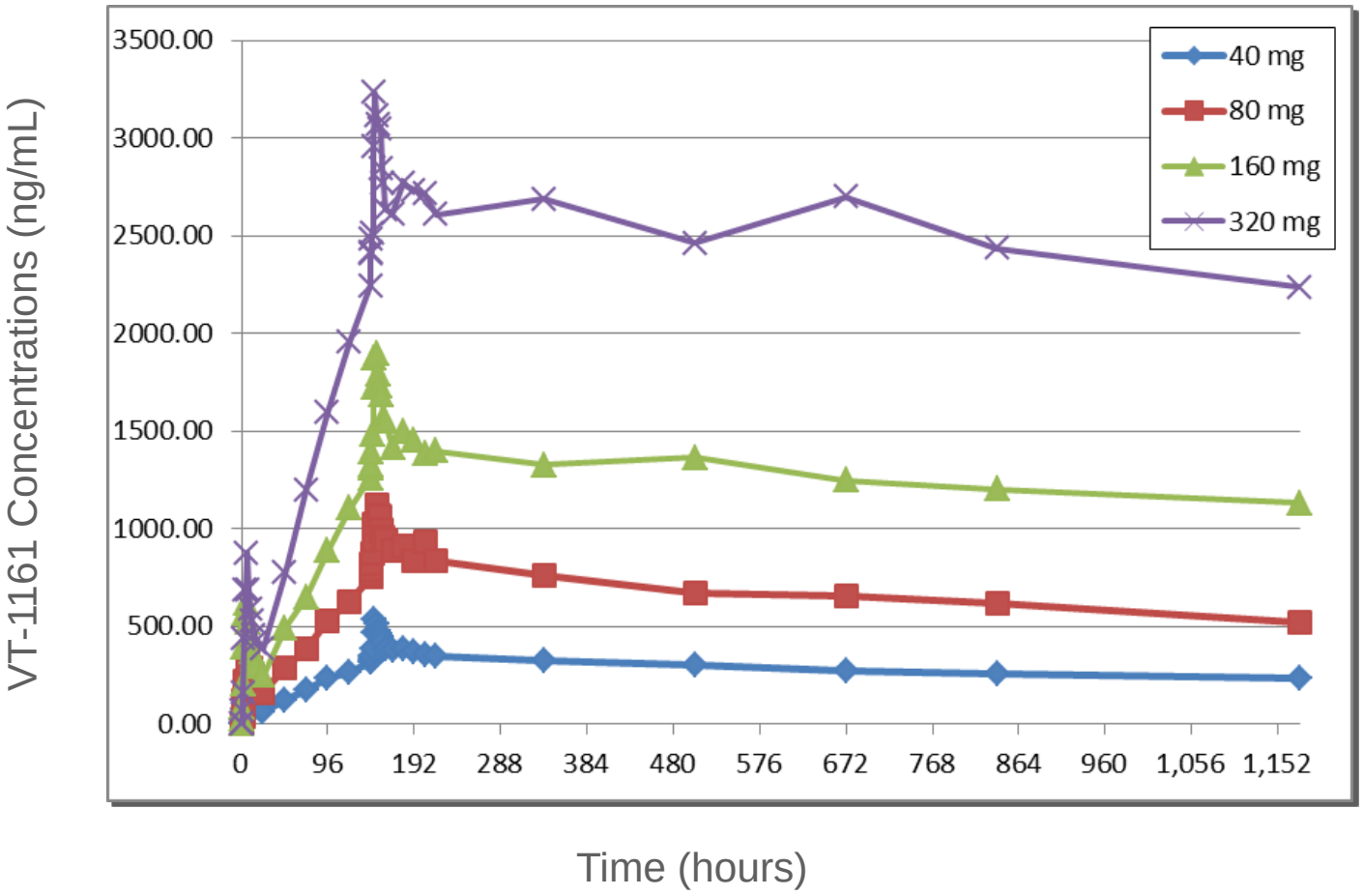
Mean Liver Parameters by Treatment Group

Study Day	Treatment / Mean Parameter														
	Placebo			40 mg			80 mg			160 mg			320 mg		
	ALT	AST	TBIL	ALT	AST	TBIL	ALT	AST	TBIL	ALT	AST	TBIL	ALT	AST	TBIL
Baseline	21.6	19.8	0.43	24.2	22.0	0.35	18.7	20.7	0.43	20.2	19.5	0.48	23.8	20.0	0.52
Day 7	19.6	18.0	0.44	18.3	16.8	0.27	17.8	17.4	0.46	22.0	18.2	0.45	20.0	17.5	0.47
Day 14	22.8	19.3	0.39	18.8	20.2	0.43	18.4	20.4	0.42	33.7	27.2	0.28	20.8	18.2	0.45
Day 28	21.3	20.1	0.44	21.5	24.3	0.37	19.2	20.7	0.42	20.0	17.8	0.45	22.5	20.3	0.50
Day 49	20.5	19.9	0.60	19.2	20.5	0.35	20.2	25.0	0.43	20.0	19.2	0.48	26.2	22.2	0.52

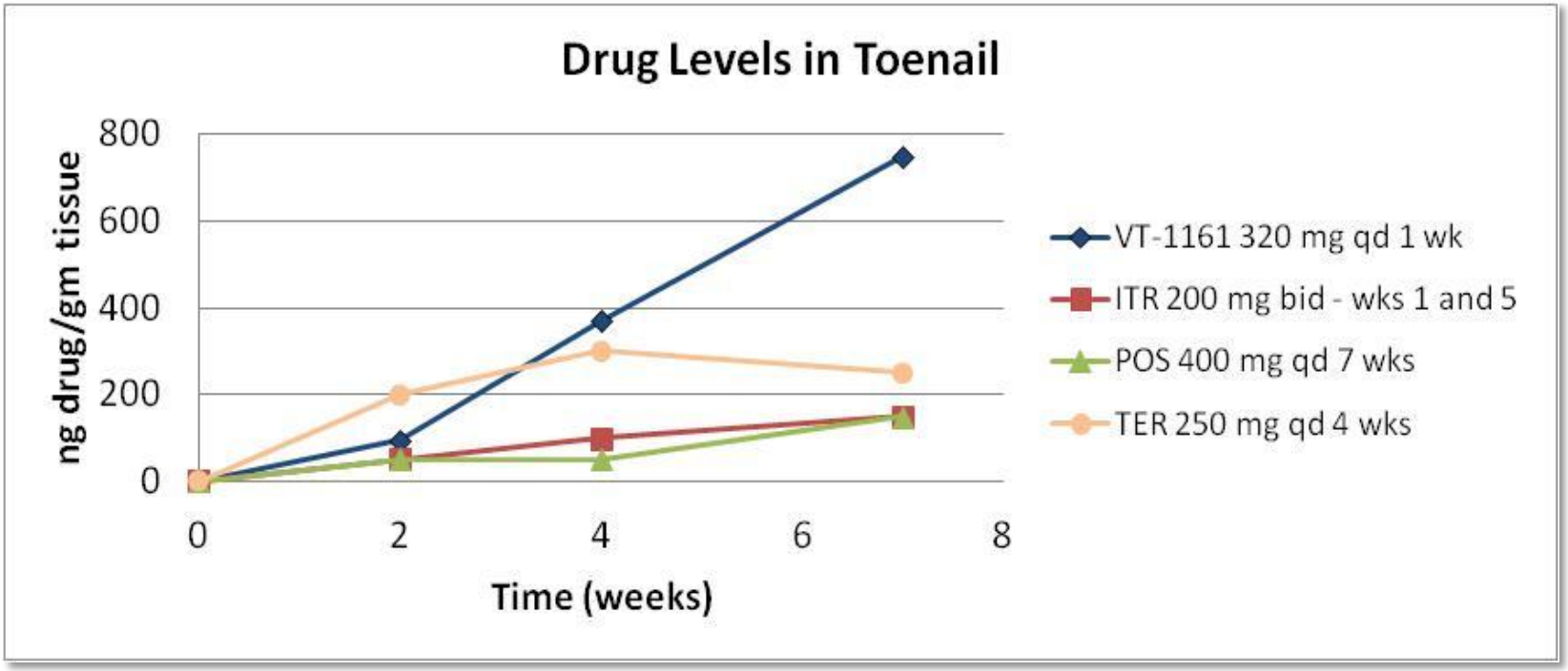
- No significant impact of VT-1161 on liver enzyme parameters

VT-1161 MAD Results: Plasma PK

- Plasma PK for VT-1161 with intense PK after Day 1 and Day 7



VT-1161 MAD Results: Tissue Levels



- Higher levels of VT-1161 were observed in toenails compared to historical data for itraconazole (ITR), posaconazole (POS), or terbinafine (TER), despite a shorter dosing regimen
- Therapeutic skin concentrations of 1388 ng/mL were achieved on Day 8

VT-1161 MAD Study Summary

- Oral VT-1161 was safe and well tolerated
- No clinically-significant, drug-related adverse events or changes in lab parameters reported
- No drug-related impact on QTc intervals
- Plasma PK was dose-proportional, with a Cmax after 7 days of 320 mg/d of approximately 3.3 µg/mL
- Excellent nail and skin penetration observed
- Phase 2 studies are planned to assess the safety and efficacy of oral VT-1161 in patients with tinea pedis and onychomycosis