A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Four Oral Dosing Regimens of VT-1161 in the Treatment of Patients with Moderate-Severe Toenail Onychomycosis (RENOVATE): Results of a Planned Week 24 Interim Analysis

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Introduction

Currently approved topical treatments for onychomycosis have low efficacy rates. Oral therapies, while more effective, suffer from liver toxicity, drug interactions, and often require blood monitoring. VT-1161 is a novel and highly selective inhibitor of fungal CYP51. In preclinical studies, VT-1161 was shown to be highly selective for fungal CYP51, with minimal activity against off-target human CYPs. VT-1161 has demonstrated potent activity against *Trichophyton rubrum* and *Trichophyton mentagrophytes*. In phase I clinical studies, VT-1161 exhibited favorable oral pharmacokinetics with sustained target tissue concentrations and a robust safety profile.

Objective

Here, we report 24-week interim results in 107 patients from our ongoing Phase 2b study to evaluate the efficacy and safety of oral VT-1161 in patients with toenail onychomycosis

Methods

RENOVATE is an ongoing Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study. The study enrolled 259 patients (18-70 years) with a clinical diagnosis of moderate to severe distal lateral subungual onychomycosis (DLSO) defined as having 25% to 75% nail involvement at baseline and positive KOH and culture for dermatophytes, performed at a central laboratory. Patients had at least 2 mm clear nail measured from the proximal nail fold and a nail thickness of no greater than 3 mm measured at the distal end. Patients receiving systemic antifungal therapy within 3 months of study entry or topical foot or toenail antifungal therapy within 1 month of study entry were excluded, as were patients with significant major organ diseases, poorly controlled diabetes or current infections other than onychomycosis. Randomization information is included in Figure 1.

Clinical Assessment:
The percent nail involvement of the target toenail was assessed by the Principal Investigator (PI) at each clinic visit both as an absolute percentage and also using an Investigator Global Assessment (IGA) according to the following scale:
0: 0% nail involvement
1: > 0% to ≤ 10% nail involvement
2: > 10% to < 25% nail involvement
3: ≥ 25% to ≤ 50% nail involvement
4: > 50% to ≤ 75% nail involvement
5: > 75% nail involvement

Mycological Assessment:
Dermatophyte infection was assessed by a potassium hydroxide (KOH) wet mount test and by culture of the subungual debris taken from the most proximal leading edge of the infection in the target toenail

Key Interim Analysis Endpoints at Week 24:
- Percent change from baseline in nail involvement
- Percent of patients with ≤10% nail involvement and ≤25% nail involvement
- Therapeutic success, defined as mycological cure (negative KOH and negative dermatophyte culture) and ≤10% nail involvement

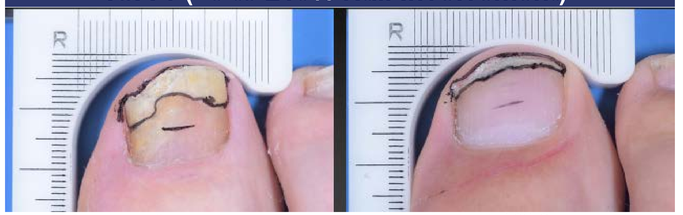
Safety Assessment:
Adverse events (AE) were collected as reported by patients as well as clinically significant changes in labs. AE were coded with the MedDRA® dictionary.

Results

IGA 2 (>10 to <25% Nail Involvement)

Baseline | Week 24/EOT

IGA 1 (>0 to ≤10% Nail Involvement)



Baseline | Week 24/EOT

IGA 0 (0% Nail Involvement)

Baseline | Week 24/EOT

Significant Improvement in all Toenails at Week 24

All five toenails are affected
Large toenail is ~65% affected

All except the large toenail are cleared
Large toenail is ~25% affected

Figure 2. Photographic documentation revealed rapid nail clearing in target toenails. Photographs were selected by a blinded assessor with no knowledge of the treatment groups.

Methods

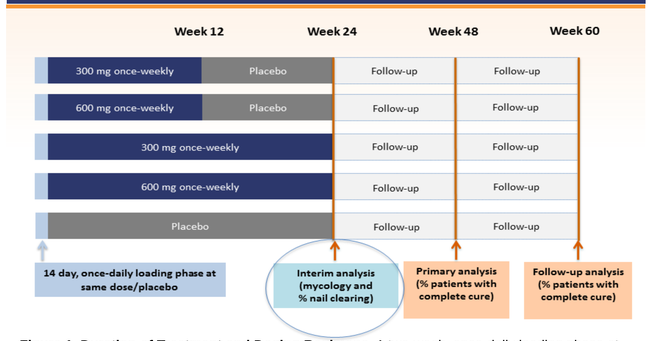


Figure 1. Duration of Treatment and Dosing Regimens. A two-week, once-daily loading phase at 300 mg, 600 mg, or placebo is followed by once-weekly dosing for ten weeks, for 12 total weeks. Participants then received either placebo or continued once-weekly dosing for 12 additional weeks, for 24 total weeks of treatment. The treatment phase was followed by a planned interim analysis at 24 weeks, reported here. The primary analysis will occur at 48 weeks and a follow-up analysis at 60 weeks.

Patient Demographics

	300 mg/ 12 Week N=23	300 mg/ 24 Week N=23	600 mg/ 12 Week N=22	600 mg/ 24 Week N=22	Placebo N=17
Mean Age (years)	48.2	47.8	47.1	48.8	50.8
Gender (% male)	78%	83%	82%	91%	88%
Race (% Caucasian)	83%	96%	82%	59%	95%
Mean Nail Involvement at Screening	47.4%	47.7%	46.7%	41.8%	43.4%
% of Patients with >50% to ≤75% Nail Involvement	26%	35%	23%	18%	18%

Patient characteristics and demographics:
A planned interim analysis was scheduled when approximately 100 patients had completed the Week 24 visit. Data were unblinded by treatment arm only; all study personnel remain blinded as to individual patient treatment assignments. Efficacy assessment is presented for 107 patients in the intent to treat population (ITT), defined as all patients who were randomized and who received at least on dose of study medication. At baseline, patients had an average of 4.8 to 5.0 toenails involved and a nail thickness of 1.8 to 2.2 mm across the treatment groups at screening.

Clinical Endpoints at Week 24

	300 mg/ 12 Week N=23	300 mg/ 24 Week N=23	600 mg/ 12 Week N=22	600 mg/ 24 Week N=22	Placebo N=17
Mean Change from Baseline in % Nail Involvement	-51.2%	-50.8%	-39.7%	-49.6%	-5.7%
Median Change from Baseline in % Nail Involvement	-66.7%	-58.3%	-37.5%	-60.8%	-16.7%
≤25% Nail Involvement (IGA 0, 1, or 2)	57%	56%	36%	60%	12%
≤10% Nail Involvement (IGA 0 or 1)	35%	26%	18%	32%	0%
Therapeutic Success*	13%	17%	9%	9%	0%

*Mycologic cure and ≤10% nail involvement

Efficacy:
After 24 weeks, patients attained a median improvement from baseline in percent nail involvement as high as 66.7% in the VT-1161 arms. Furthermore, up to 60% of patients had ≤25% nail involvement and up to 35% had ≤10% nail involvement after only 24 weeks in the study (See table above).
The mycology data revealed rapid eradication of dermatophytes with up to 60% of cultures being negative after 24 weeks, and with mycologic cure achieved in 23%-35% of patients across the VT-1161 arms.

Safety and Tolerability:
VT-1161 was very well tolerated through the week 24 interim analysis. A total of 47 treatment-emergent adverse events (TEAE) were reported, most of which were mild to moderate in severity and which occurred with similar frequency across all arms, including the placebo arm. The most commonly reported TEAEs were nausea, diarrhea and upper respiratory infection. Only eight subjects reported TEAE across all arms as possibly to definitely related to study drug by the blinded investigator. In addition, there were no drug-related serious AE reported and no patient discontinued the study due to a laboratory abnormality. There was no evidence of an adverse effect of VT-1161 on liver function.

Summary and Conclusion

- In this interim analysis, VT-1161 has demonstrated strong evidence of clinical efficacy in patients through 24 weeks of the study.
- Patients in all treatment arms demonstrated substantial nail improvement compared to placebo. The rate of nail clearing through 24 weeks was exceptional given the slow rate of toenail growth.
- At all doses evaluated, VT-1161 was safe and very well tolerated and there was no evidence of an adverse effect on liver function.

High potency, broad therapeutic index, and favorable oral pharmacokinetic properties suggest VT-1161 has excellent potential as a safe and effective treatment for onychomycosis.

Sponsorship: This poster is sponsored by Viamet Pharmaceuticals, Inc., Durham, NC