Efficacy and Safety of VT-1161 in a Randomized, Double-Blind, Placebo-Controlled Study of Four Oral VT-1161 Regimens in the Treatment of Patients with Moderate-to-Severe Distal-Lateral Subungual Onychomycosis (DLSO)

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Introduction

Current therapies for onychomycosis are inadequate due to the low efficacy of topical products or poor safety profile of oral therapies, which often require monitoring of liver transaminases. VT-1161 is a novel inhibitor of cytochrome P51 (CYP51), with nearly 2000-fold greater selectivity for fungal CYP51, and minimal activity against off-target human CYPs. It exhibits favorable oral pharmacokinetics with sustained plasma and nail concentrations combined with an excellent safety profile. VT-1161 has demonstrated potent activity against *Trichophyton rubrum*, *T. mentagrophytes*, and yeast.

Objective

We report the final results of RENOVATE, a Phase 2b study to evaluate the efficacy and safety of oral VT-1161 in patients with toenail onychomycosis.

Methods

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 who were breast feeding, pregnant or intended to become pregnant were excluded. Those who received systemic antifungal therapy for 3 months, or a topical applied to their toenail or feet for 1 month prior to entry were also excluded.

Treatment:
Patients received 300 or 600 mg oral VT-1161 or matching placebo once-weekly for either 10 or 22 weeks, following 14-days of a daily loading dose.

Clinical Assessment:
The percent nail involvement of the target toenail was assessed by the Principal Investigator (PI) at each clinic visit.

Mycological Assessment:
Dermatophyte infection was assessed by KOH wet mount microscopy and culture of the subungual debris in the target toenail; both conducted at the central mycology Lab.

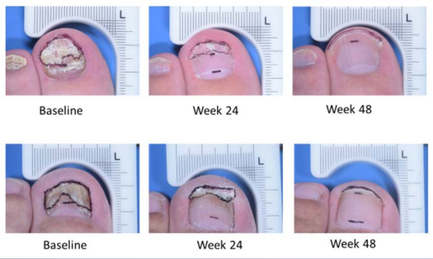
Efficacy Endpoints and Assessments:
The primary efficacy endpoint was the proportion of patients with complete cure at Week 48, defined as both clinical cure (0% nail involvement) and mycological cure (negative KOH stain and negative culture). The secondary endpoints were complete cure at Week 60, mycological and clinical cure at Week 48 and/or 60. Efficacy assessment are presented for 259 patients in the intent to treat (ITT) population defined as all patients who were randomized.

Safety Assessment:
Adverse events (AE) were collected as reported by patients as well as by any clinically significant changes in blood chemistry. ECGs performed at each visit.

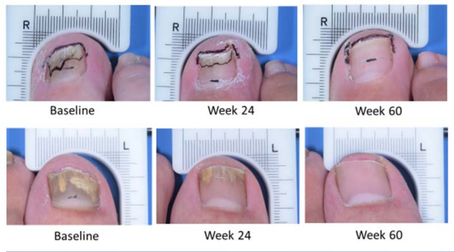
Statistics:
Study was designed to provide >90% power to show a treatment difference of 25% between active treatment and placebo in complete cure rates at Week 48 (Fisher's exact test, two-sided alpha=0.05; assuming 5% of placebo patients are completely cured)

Results

VT-1161: RENOVATE Photos Patients # 1 and 2



VT-1161: RENOVATE Photos Patients # 3 and 4



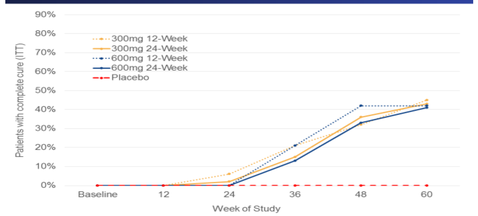
Adverse Events Through Week 60- ITT

AEs and Discontinuation Rates Comparable to Placebo

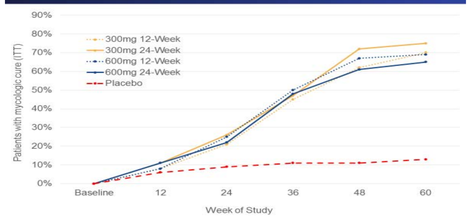
	300 mg/ 12 Week N=53	300 mg/ 24 Week N=53	600 mg/ 12 Week N=52	600 mg/ 24 Week N=54	Placebo N=47
Any Treatment-Emergent Adverse Event	55%	49%	60%	67%	55%
Any Related Treatment-Emergent AE	6%	6%	8%	11%	6%
Discontinued Study N (%)	6 (11%)	5 (9%)	10 (19%)	11 (20%)	5 (11%)
Discontinued Study Due to Lab Abnormality N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinued Study Due to AE N (%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)

The two adverse events leading to discontinuation in the two high doses were nausea and muscle spasm each in 1 patient only

VT-1161 Provides Improved Efficacy Over Time



VT-1161 Provides Sustained Mycological Cures



ITT Complete Cure Rates of Approved Agents

VT-1161 Vs. Marketed Onychomycosis Agents: ITT Analyses

VT-1161 RENOVATE Data	Lamisil[1] 250 mg QD for 12 wks	Onmel[2] 200 mg QD for 12 wks	Jublia[3] 10% QD for 48 wks	Kerydin[3] 5% QD for 48 wks	Penlac[4] 8% QD for 48 wks
32-40%	31%	22.3%	17.8% and 15.2%	6.5% and 9.1%	5.5% And 8.5%

[1] Per the US NDA; assessment at 48 weeks
[2] Novel itraconazole formulation; per the US package insert; assessment at 48 weeks
[3] Per the US Package Insert; assessment at 52 weeks
[4] Per the US Package Insert; assessment at 48 weeks

The data comparison is for illustration purpose only

Clinical and Safety Outcomes

Efficacy:
After 48 weeks, patients attained a median improvement from baseline in percent nail involvement as high as 92% in the VT-1161 arms vs 13% in the placebo arm. Furthermore, up to 74% of patients had ≤10% nail involvement after 48 weeks in the study.

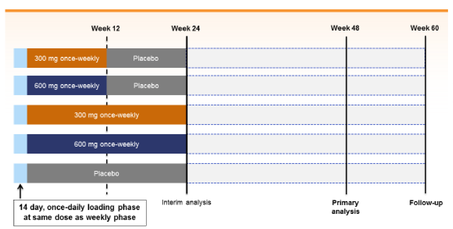
The mycology data revealed rapid eradication of dermatophytes with up to 81% of cultures being negative after 48 weeks, and with mycologic cure (negative KOH and negative culture) achieved in 61%-72% of patients across the VT-1161 arms.

All cure rates increased from Week 48 to 60. A PK and safety extension study with 155 patients is ongoing and data is expected in 3Q 2017.

Safety and Tolerability:
VT-1161 was very well tolerated through Week 60. The treatment-emergent adverse events (TEAE) reported by greater than 5 patients were ingrown toenail, dermatitis, headache, and cough, were mild to moderate in severity and occurred with similar frequency across all arms, including the placebo arm. The TEAEs noted as possibly to definitely related to study drug were nausea (2%), constipation (2%) and dysgeusia (2%) across all VT-1161 arms, as determined by the blinded investigator. In addition, there were no drug-related serious AEs reported and no patient discontinued the study due to a laboratory abnormality (as shown). There was no evidence of an adverse effect of VT-1161 on liver function, or QT intervals.

Study Design

RENOVATE Study Design



Four active arms included: 300 mg or 600 mg for 12 or 24 weeks. All patients were randomized to once-daily dosing for first 2 weeks, then switching to once-weekly thereafter. The placebo group received matching placebo VT-1161 tablets for 24 weeks.

Patient Demographics

Baseline Demographics- ITT

Patient Characteristics Consistent with Moderate to Severe OM

	300 mg/ 12 Week N=53	300 mg/ 24 Week N=53	600 mg/ 12 Week N=52	600 mg/ 24 Week N=54	Placebo N=47
Mean Age (years)	48.8	50.4	49.4	49.0	52.7
Gender (% male)	77%	85%	75%	83%	81%
Race (% Caucasian)	85%	87%	81%	78%	87%
% Nail Involvement at Screening	47.2%	44.4%	45.8%	45.8%	46%
Number of Affected Toenails at Screening	4.7	4.3	5.0	4.6	4.7

Patients' baseline characteristics were similar across all treatment groups. Consistent with other onychomycosis trials, Most patients were male Caucasians. The percent nail involvement of the target toenail and the average number of affected toenails suggest moderate to severe onychomycosis .

Summary and Conclusions

- Therapeutic plasma concentrations of VT-1161 were rapidly and safely achieved
- Results suggest once-weekly dosing provides for an ideal regimen to maintain effective plasma exposures that are associated with excellent nail concentrations through Week 60.
- Given the long half-life of VT-1161, it is projected that high plasma and nail concentrations will be present well beyond the Week 48 endpoint.
- Plasma and nail PK data are far superior to known oral agents including terbinafine
- Dystrophic nails, nails with dermatophytoma or with spikes responded remarkably well as shown in the nail photographs.
- VT-1161 cure rates were higher than all other antifungal drugs approved for treatment of OM including terbinafine.

High potency, broad therapeutic index, and favorable oral pharmacokinetic properties suggest VT-1161 has a great potential as a safe and effective treatment for onychomycosis. Phase 3 studies are being planned for 3Q 2017.