

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 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 a 14-days of 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 a KOH wet mount microscopy and by culture of the subungual debris in the target toenail both conducted at the central mycology Lab.

Efficacy Endpoints:

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 mycological cure, clinical cure and at Week 48 and 60.

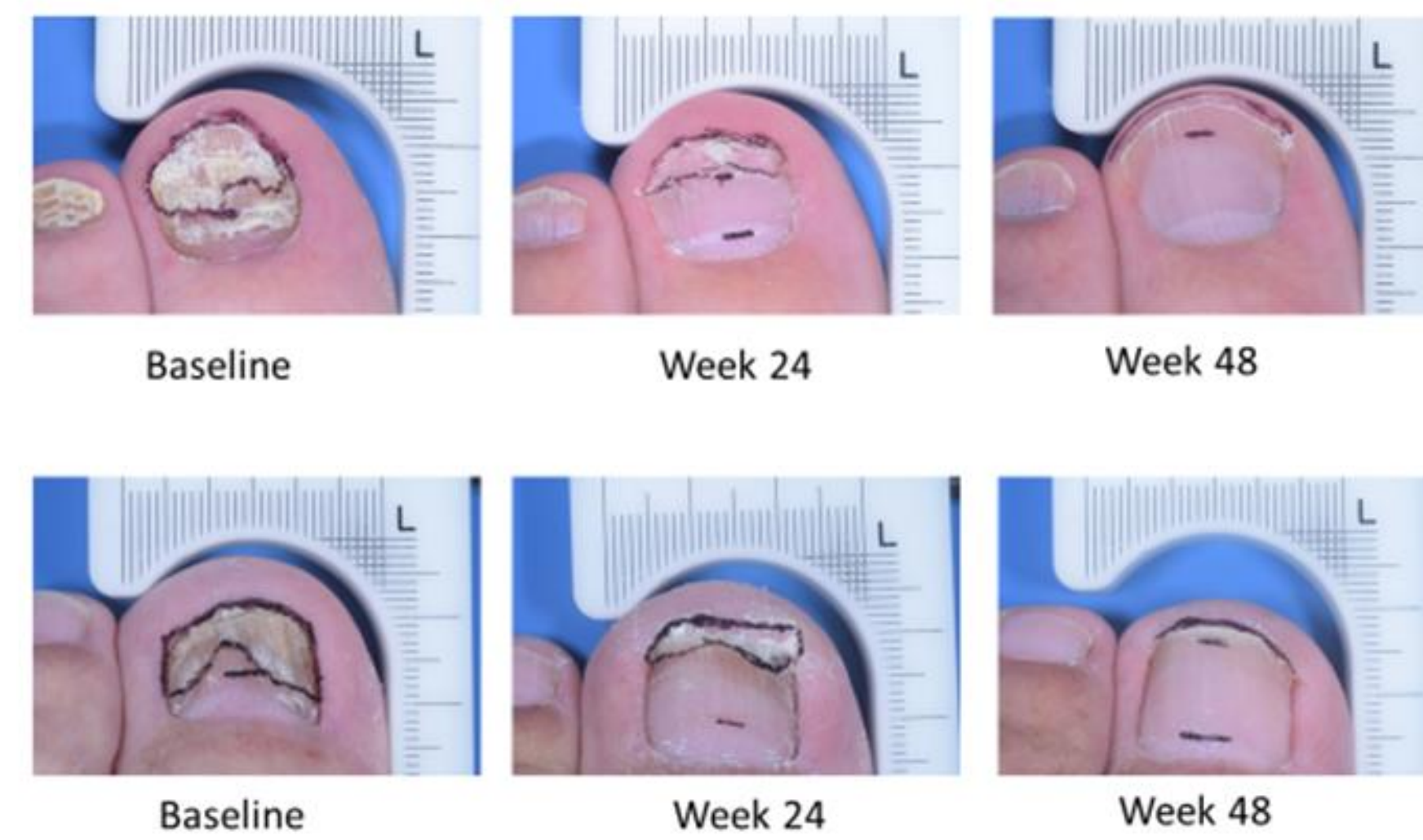
Efficacy assessment are presented for 259 patients in the intent to treat (ITT) population defined as all patients who were randomized and received at least on dose of study medication.

Statistics

Study was designed to provides >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

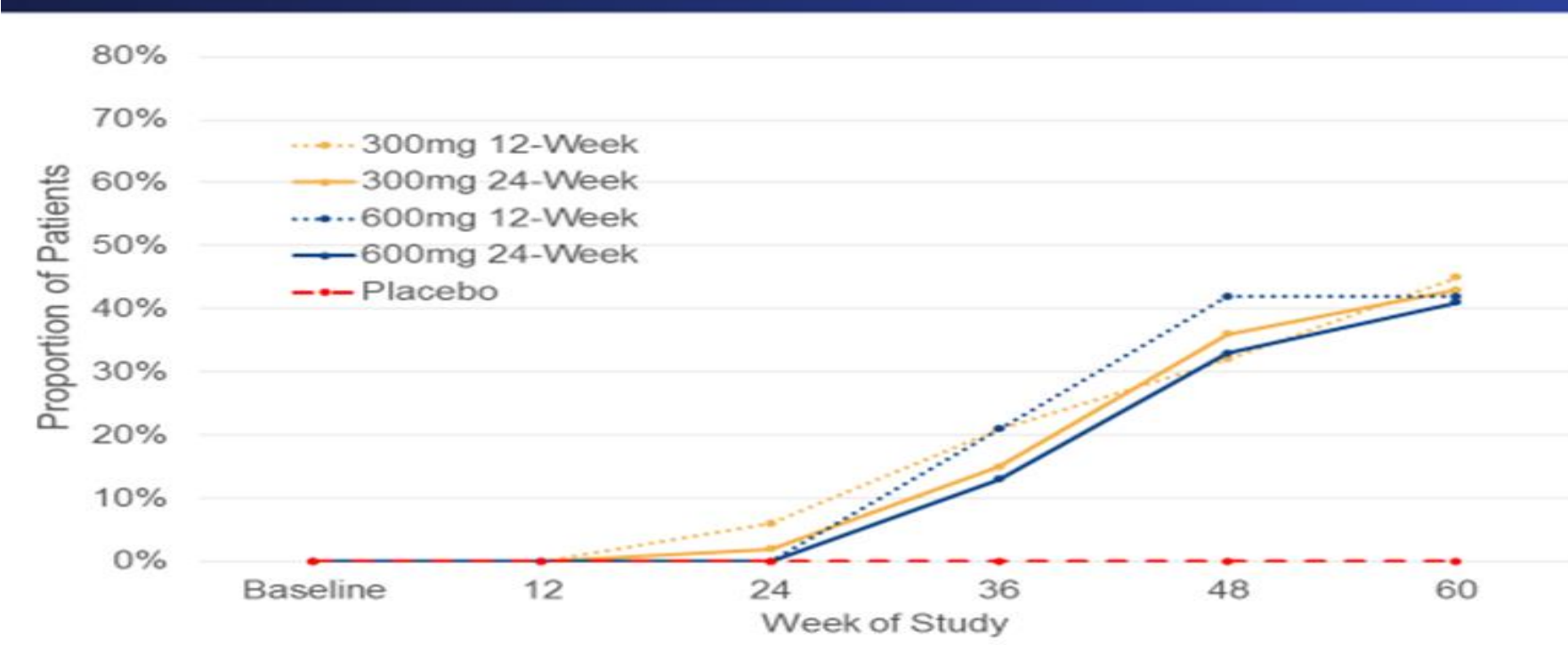
VT-1161: RENOVATE Photos Patients # 1 and 2



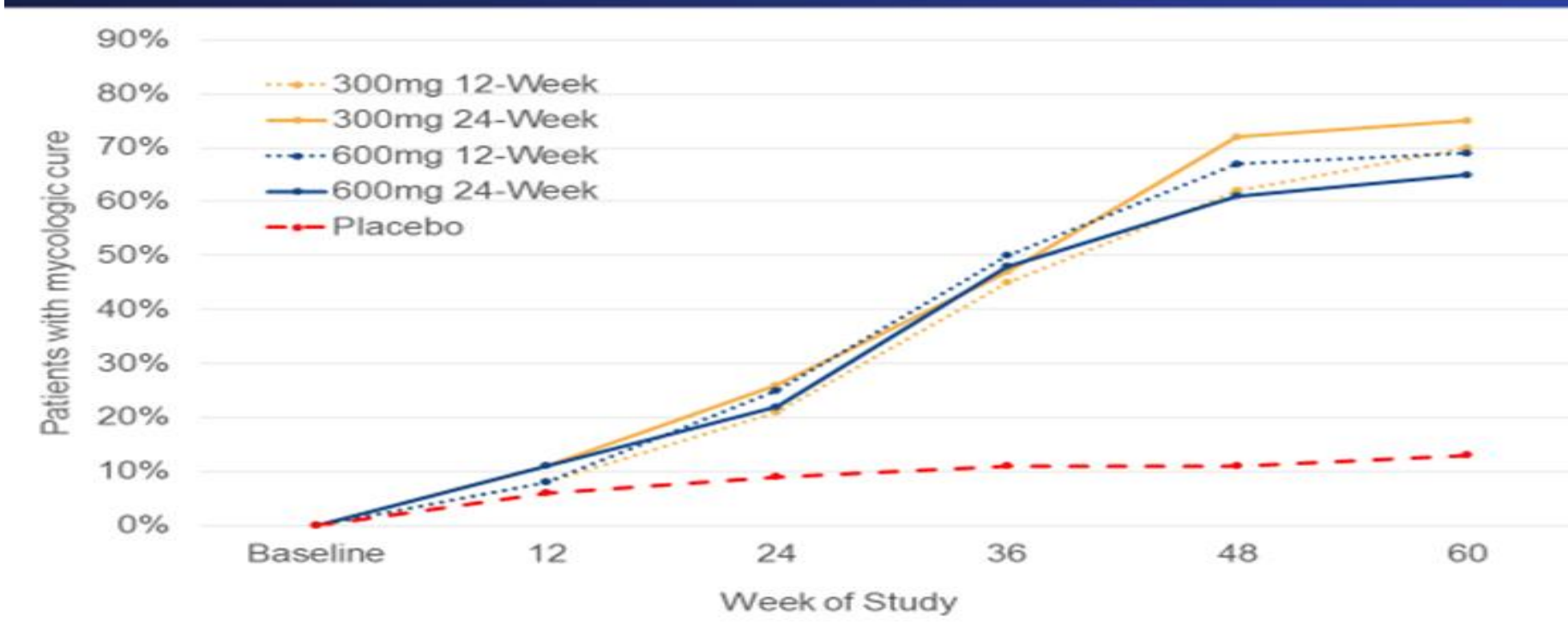
VT-1161: RENOVATE Photos Patients # 3 and 4



Complete Cure Over Time- ITT



Mycologic Cure Over Time- ITT



Adverse Events Through Week 60- Summary

Adverse Events Through Week 60- ITT Population					
	300 mg/ 12 Week	300 mg/ 24 Week	600 mg/ 12 Week	600 mg/ 24 Week	Placebo
Any Treatment-Emergent Adverse Event	55%	49%	60%	67%	55%
Any Related Treatment-Emergent Adverse Event	6%	6%	8%	11%	6%
Any Serious Adverse Event	2%	2%	4%	9%	4%
Any Related Serious Adverse Event	0%	0%	0%	0%	0%
Discontinuation of Study Drug Due to Adverse Event	0%	2%	4%	6%	2%

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ITT Complete Cure Rates of Approved Agents

VT-1161 Vs. Marketed Onychomycosis Agents: ITT Analyses					
VT-1161 RENOVATE Data	Lamisil ¹	Onmel ²	Jublia ³	Kerydin ²	Penlac ⁴
250 mg QD for 12 wks	200 mg QD for 12 wks	10% QD for 48 wks	5% QD for 48 wks	6% QD for 48 wks	5% QD for 48 wks
32.40%	31%	22.3%	17.8% and 15.2%	6.5% and 9.1%	5.5% and 8.2%

¹ Per the US NDA; assessment at 48 weeks
² Novel Imazazole 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

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Clinical & Safety Outcomes

Efficacy:

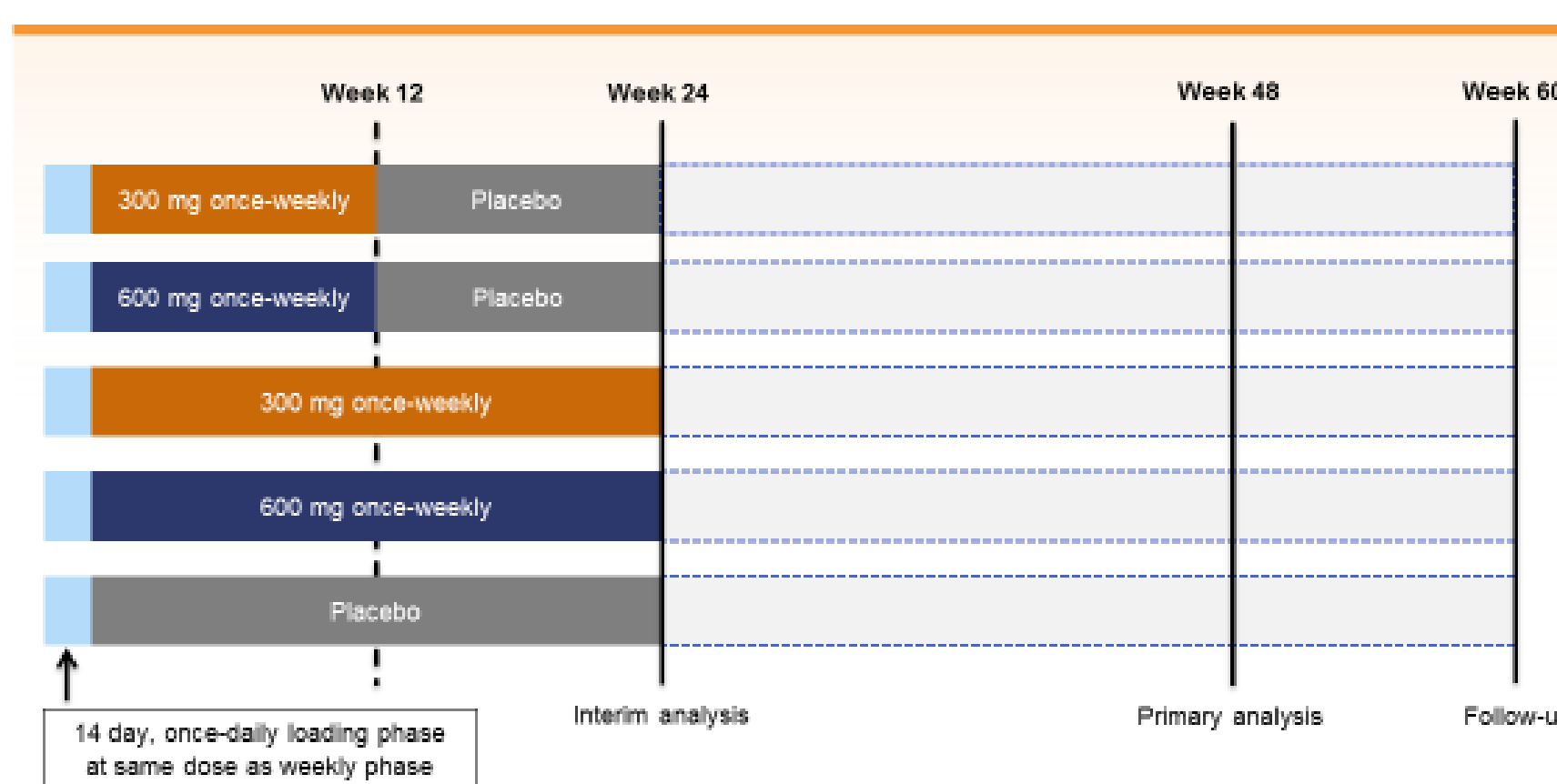
After 48 weeks, patients attained a median improvement from baseline in percent nail involvement as high as 92% in the VT-1161 arms vs 13% in placebo. Furthermore, up to 74% of patients had ≤10% nail involvement after 48 weeks in the study. The mycology data revealed rapid eradication of dermatophytes 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. In addition, a PK and safety extension study with 156 patients is ongoing and data is expected in 3Q 2017.

Safety and Tolerability:

VT-1161 was very well tolerated through the week 60. The treatment-emergent adverse events (TEAE) reported by greater than 5 patients were ingrown toenail, dermatitis, headache, and cough and were mild to moderate in severity and occurred with similar frequency across all arms, including the placebo arm. The notable TEAE 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 AE 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

VT-1161: RENOVATE Study Design



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4 active arms: 300 mg or 600 mg for 12 or 24 weeks. Once-daily dosing for first 2 weeks, then switching to once-weekly thereafter. Placebo group received matching placebo VT-1161 tablets.

Patient Demographics

Baseline Demographics

Baseline Demographics- ITT Population					
	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 (% involved)	47.2%	44.4%	45.8%	45.8%	48%
Number of Affected Toenails at Screening	4.7	4.3	5.0	4.6	4.7

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

Summary and Conclusions

- Due to the high therapeutic ratio of VT-1161, high plasma concentrations were rapidly and safely achieved
- Once-weekly dosing is ideal to maintain effective plasma exposures that is 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 Lamisil
- Dystrophic nails, nails with dermatophytoma or with spikes responded remarkably well as shown in the nail photographs

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 3Q2017