VT-1161 Dosed Once Daily or Once Weekly Exhibits Potent Efficacy in Treatment of Dermatophytosis in a Guinea Pig Model

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Current therapies used to treat dermatophytoses such as onychomycosis are effective but display room for improvement in efficacy, safety, and convenience of dosing. We report here that the investigational agent VT-1161 displays potent *in vitro* antifungal activity against dermatophytes, with MIC values in the range of ≤ 0.016 to $0.5 \mu\text{g/ml}$. In pharmacokinetic studies supporting testing in a guinea pig model of dermatophytosis, VT-1161 plasma concentrations following single oral doses were dose proportional and persisted at or above the MIC values for at least 48 h, indicating potential *in vivo* efficacy with once-daily and possibly once-weekly dosing. Subsequently, in a guinea pig dermatophytosis model utilizing *Trichophyton mentagrophytes* and at oral doses of 5, 10, or 25 mg/kg of body weight once daily or 70 mg/kg once weekly, VT-1161 was statistically superior to untreated controls in fungal burden reduction ($P < 0.001$) and improvement in clinical scores ($P < 0.001$). The efficacy profile of VT-1161 was equivalent to those for doses and regimens of itraconazole and terbinafine except that VT-1161 was superior to itraconazole when each drug was dosed once weekly ($P < 0.05$). VT-1161 was distributed into skin and hair, with plasma and tissue concentrations in all treatment and regimen groups ranging from 0.8 to $40 \mu\text{g/ml}$ (or $\mu\text{g/g}$), at or above the MIC against the isolate used in the model ($0.5 \mu\text{g/ml}$). These data strongly support the clinical development of VT-1161 for the oral treatment of onychomycosis using either once-daily or once-weekly dosing regimens.

Fungal infections of the skin, nails, and hair by dermatophytes, yeasts, and nondermatophyte molds are a common occurrence (1–3), with an estimated worldwide prevalence of 20% to 25% (1). In a survey of ambulatory records in the United States, these infections necessitated an average of 4 million physician visits per year from 1995 to 2004 (4), and the majority of these infections were caused by dermatophytes. The worldwide distribution of causative fungi and types of infection are dependent on geography, environment, and cultural factors (1, 2). Consistent with most of Europe and the United States (1, 2), a recent retrospective study found that onychomycosis (also referred to as tinea unguium) was the most common dermatophyte infection and that the absolute number of onychomycosis cases increased 10-fold over a 40-year period (5). This increase can be partly explained by the increases of two at-risk populations, the elderly (6) and diabetics (7). The most common species causing onychomycosis in Europe and the United States are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* (8).

Current oral treatment options for superficial fungal infections include allylamines, such as terbinafine, and azole-based fungal sterol 14α -demethylase (CYP51) inhibitors (8, 9). The azoles fall into two classes defined by the moiety that binds the heme iron within the active site of CYP51, the imidazoles (e.g., ketoconazole), which are rarely used orally due to poor systemic side effect profiles, and the triazoles (e.g., itraconazole). These heterocycles greatly aid in the potency of inhibiting fungal CYP51 but are relatively nonselective and can lead to inhibition of off-target human CYPs, often manifested as side effects. Although allylamines and azoles are efficacious for a large number of dermatophyte infections, there remains room for improvement in efficacy and safety, particularly for more difficult-to-treat infections such as onychomycosis. In randomized controlled trials of onychomycosis, complete cure rates reflecting both mycological and clinical cures for terbinafine and itraconazole range from approximately 35 to 50% (10). Moreover, both drug classes carry

safety warnings pertaining to liver toxicity (11, 12) and drug-drug interactions (13), with a small but significant percentage of more serious side effects (14–16). As a consequence, many patients choose not to pursue oral therapy.

Given the need for improved efficacy and a better safety profile, the lack of new oral therapies under development is striking. It has been 18 years since the last new oral drug (terbinafine) was approved by the FDA for the treatment of onychomycosis. Additionally, since 1996, only three phase 2 studies of new oral therapies have been reported (ravuconazole [17], posaconazole [18], and albaconazole [19]). Although these studies were successful in demonstrating efficacy, complete cure rates were similar to current standard-of-care therapies (17–19), and no further clinical studies on these agents have been reported.

We recently described a novel fungal CYP51 inhibitor, VT-1161 (Fig. 1), that uses a tetrazole to bind the heme iron within the enzyme's active site (20). The tetrazole was critical in establishing greater selectivity for fungal CYP51 versus off-target human CYPs while retaining high potency for the fungal CYP51 target. The potency of VT-1161 against *Candida albicans* CYP51 in a cellular assay was ≤ 0.5 nM compared to *in vitro* 50% inhibitory concen-

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FIG 1 Chemical structure of VT-1161.

tration (IC_{50}) values of ~ 100 μM or greater against human CYP51 and key xenobiotic-metabolizing CYPs present in human liver microsomes (e.g., CYP2C9, -2C19, and -3A4) (21). VT-1161 has also demonstrated potent intrinsic activity against the dermatophyte *T. rubrum* (20). In this study, we show that *in vitro*, the antifungal activity of VT-1161 translated into potent activity in the oral treatment of dermatophytosis in a guinea pig model, and that the efficacy of VT-1161 was statistically equivalent whether dosed once daily or once weekly.

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MATERIALS AND METHODS

Materials. (i) Guinea pigs. Male albino Sprague-Dawley guinea pigs were obtained from Harlan (Indianapolis, IN).

(ii) Dermatophyte isolates. The dermatophyte strains used in this study (see Table 1) were obtained from the culture collection housed at the Center for Medical Mycology (University Hospitals Case Medical Center/Case Western Reserve University, Cleveland, OH). Cultures were maintained on potato dextrose agar (PDA) at $-80^{\circ}C$. When needed, the strains were thawed and grown on Sabouraud dextrose agar (Difco Laboratories, Detroit, MI).

(iii) Antifungal agents. VT-1161 was supplied by Viamet Pharmaceuticals, Inc. (Durham, NC), and itraconazole, terbinafine, and Cremophor EL (used to prepare the drug for oral delivery) were purchased from Sigma-Aldrich (St. Louis, MO).

***In vitro* susceptibility testing.** Antifungal susceptibility tests were performed using a broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M38-A2 methodology (22). The concentration range of test compounds was 0.016 to 8 $\mu g/ml$. Inocula were prepared in RPMI 1640 to a concentration of 1×10^3 to 3×10^3 CFU/ml and added to drug dilutions, and the mixtures were incubated at $35^{\circ}C$ for 4 days. The MIC endpoint was defined as the lowest concentration of inhibitor causing 80% reduction of growth compared to control. *T. rubrum* ATCC MYA-4438 and *T. mentagrophytes* ATCC MYA-4439 were used as dermatophyte quality control (QC) organisms as recommended by CLSI.

Pharmacokinetic studies. Single-dose oral pharmacokinetics (PK) of VT-1161 were determined in female Dunkin-Hartley guinea pigs at Washington Biotechnology (Baltimore, MD). A dose of 5 or 25 mg/kg of body weight in 20% Cremophor EL was administered by oral gavage ($n = 4$), and blood samples were collected at 0, 0.5, 1, 2, 4, 8, 24, and 48 h. Cremophor EL was used to provide higher exposures (data not shown). Plasma was separated, frozen, stored at $-80^{\circ}C$, and shipped to OpAns, LLC (Durham, NC) for determination of VT-1161 plasma concentrations.

Guinea pig dermatophytosis model. The dermatophytosis model was described previously (23). *T. mentagrophytes* ATCC 24953 isolates were subcultured on PDA plates and incubated at $30^{\circ}C$ for 5 days. (MIC values for the test compounds against this isolate were 0.5, 0.25, and 0.03 $\mu g/ml$ for VT-1161, itraconazole, and terbinafine, respectively.) Colonies were collected, washed with sterile saline solution (0.85% NaCl), and resuspended in the same solution at a concentration of 1×10^7 CFU/100 μl .

Prior to inoculation, each animal was anesthetized intramuscularly with 0.2 ml of xylazine-ketamine-acepromazine (3:3:1, by volume). Hair was clipped on the left side of the back using an electric razor, followed by a closer shave with a disposable razor. Using a stencil, a square of 2.5 cm by 2.5 cm was marked, and the skin inside the square was abraded with sterile fine-grit sandpaper. (Sandpaper squares were cut to size, placed in a pouch and sterilized by autoclaving.) A cell suspension containing 1×10^7 conidia in 100 μl of saline was applied and rubbed thoroughly on the abraded skin. Treatment by oral gavage began 2 h postchallenge. Analyses consisted of a clinical evaluation (using a score from 0 to 5 [ranging from no lesions or hair damage to large areas of redness, scaling, and baldness to extensive damage to the integument and complete loss of hair]), mycological evaluation of hair samples, and collection of blood, skin, and hair samples for compound level evaluation (samples were stored and shipped at $-80^{\circ}C$). For mycological evaluation, 10 strands of hair were removed with sterile forceps, inoculated on PDA plates, and incubated at $30^{\circ}C$ for 2 days. Fungal growth at the hair root was examined under a stereomicroscope, and each hair was scored positive or negative for fungus. The effectiveness of the compound in each clinical evaluation and also in reducing the number of mycologically positive hair samples was expressed as a percentage relative to that in the untreated control group using the following equation: % efficacy = $100 - (T \times 100/K)$, where T is the score of the test group, and K is the score of the untreated control group.

Three separate studies were undertaken. Each treatment group had 5 animals, and all treatments were by oral gavage. In the first two studies, treatments were dosed over 9 days, with evaluations on day 10. In the third study, treatments were dosed over 13 days, with evaluations on day 13. In the first study, treatment groups were treated once daily with 75 mg/kg VT-1161, itraconazole, or terbinafine, with control groups administered vehicle alone (20% Cremophor EL) or left untreated. In the second study, treatment groups were treated once daily with 5, 10, or 25 mg/kg VT-1161 and 10- or 25-mg/kg itraconazole, with control groups administered vehicle alone or left untreated. In the third study where the treatment period was extended to 13 days, treatment groups were given VT-1161, itraconazole, or terbinafine at a dose of 10 mg/kg once daily or 70 mg/kg once weekly (i.e., on days 1 and 8). Control groups consisted of animals dosed once daily with vehicle alone and untreated animals. Note that the investigators were not blinded to the treatment groups.

Drug concentration analyses. Collected samples were analyzed using liquid chromatography-tandem mass spectrometry (LC/MS-MS) with electrospray ionization, with quantification against an external calibration curve generated in the same matrix and using the signal response ratio between the sample and the internal standard. Skin and hair samples

TABLE 1 VT-1161 and itraconazole MICs against dermatophytes

Dermatophyte strain	MIC ($\mu g/ml$) for:	
	VT-1161	Itraconazole
<i>T. rubrum</i>		
28152	≤ 0.016	0.5
28153	≤ 0.016	0.12
28170	≤ 0.016	0.25
28171	≤ 0.016	0.06
<i>T. mentagrophytes</i>		
19723	≤ 0.016	0.06
24953	0.5	0.25
29775	≤ 0.016	0.06
30094	≤ 0.016	0.06
<i>E. floccosum</i>		
17626	0.03	0.03
17910	≤ 0.016	0.12
27738	0.016	0.03

FIG 2 VT-1161 oral pharmacokinetics in the guinea pig. A single dose of VT-1161 at 5 or 25 mg/kg in 20% Cremophor EL was given by oral gavage to female Dunkin-Hartley guinea pigs, and plasma samples were collected up to 48 h after the doses were administered.

were homogenized in 50 mM phosphate-buffered saline with a Brinkman Polytron PT10/35 homogenizer fitted with a 12-mm sawtooth generator, and then the compound was extracted with methyl tert-butyl ether (MTBE). Similarly, the compound was extracted from plasma samples with MTBE. Note that for itraconazole, the concentration of only the parent molecule was determined; the hydroxy metabolite, which is known to have antifungal activity (24), was not measured.

Statistical analyses of *in vivo* data. One-way analysis of variance (ANOVA) with the Bonferroni *post hoc* test was used to determine statistical significance. Analyses were performed by using SPSS for Windows version 19.0 (SPSS, Chicago, IL), and a *P* value of <0.05 was considered statistically significant.

RESULTS

VT-1161 MICs against dermatophytes. In an initial screen to determine its antifungal activity against dermatophytes, VT-1161 was tested in microdilution assays against clinical isolates of the most common causes of human onychomycosis: *T. rubrum*, *T. mentagrophytes*, and *E. floccosum* (Table 1). The MIC values for VT-1161 against the 11 isolates tested ranged from ≤0.016 µg/ml to 0.5 µg/ml, similar to those of the in-assay positive comparator itraconazole (0.03 to 0.5 µg/ml). The MIC₅₀ and MIC₉₀ values for VT-1161 were ≤0.016 and 0.03 µg/ml, respectively, while those for itraconazole were 0.06 and 0.25 µg/ml, respectively.

Pharmacokinetics of VT-1161 in guinea pigs. In preparation

for efficacy studies in this species, single oral doses of 5 and 25 mg/kg VT-1161 in 20% Cremophor EL were administered to guinea pigs, and plasma concentrations were measured for up to 48 h (Fig. 2). Exposures were high and approximately dose proportional, and the pharmacokinetic half-life was long (≥48 h), with an accurate value not determined due to the lack of sufficient concentrations at extended time points. This profile of high VT-1161 exposures and long half-lives has been observed in all animal species tested to date (E. P. Garvey, W. J. Hoekstra, and R. J. Schotzinger, unpublished data).

Efficacy of once-daily VT-1161 in a guinea pig model of dermatophytosis. VT-1161 was initially dosed orally once daily for 9 days at 75 mg/kg in a model of dermatophytosis in guinea pigs infected with *T. mentagrophytes*. The same doses of itraconazole and terbinafine were used as positive comparators, and vehicle-treated or untreated guinea pigs served as negative controls. All treatment groups demonstrated clinical (ranging from 85% to 90%) and mycological (ranging from 86% to 100%) efficacies that were each highly statistically significant compared to those in the untreated control group (*P* < 0.001) (data not shown). There were no significant differences between the active treatment groups. The vehicle control group was not significantly different than the untreated control group. Finally, in all studies reported, there were no clinical side effects in any of the treatment groups, including the vehicle control.

In a subsequent study, VT-1161 was administered at 5, 10, or 25 mg/kg orally once daily in the same model, with 10 or 25 mg/kg oral itraconazole once daily as the positive comparator, and vehicle or untreated guinea pigs serving as negative controls. All active treatment groups demonstrated clinical and mycological efficacies (Table 2) that were statistically superior to that in the untreated control group (*P* < 0.001). There were no significant differences between active treatment groups when comparing the clinical scores. However, each group receiving VT-1161 had statistically greater suppression of hair fungal burden than the 25-mg/kg itraconazole group (*P* < 0.05). In this study, there were no significant differences between doses of VT-1161 or doses of itraconazole, suggesting that the low dose for each antifungal agent had reached a maximal effect. Finally, animals treated with vehicle only were not significantly different than untreated animals in either assessment.

The drug concentrations of VT-1161 and itraconazole in plasma, skin, and hair following once-daily oral treatment for 9

TABLE 2 Efficacy of once-daily VT-1161 in guinea pigs dermatophytosis

Once-daily treatment group	Efficacy (%) ^a		Compound level ^b		
	Clinical	Mycological	Plasma (µg/ml)	Skin (µg/g)	Hair (µg/g)
5 mg/kg VT-1161	57	89 ^c	0.8 (0.4)	8 (3)	2 (2)
10 mg/kg VT-1161	68	86 ^c	2.3 (0.4)	19 (3)	5 (3)
25 mg/kg VT-1161	61	91 ^c	6.3 (0.5)	40 (3)	8 (3)
10 mg/kg itraconazole	78	52	<0.02 ^d	1.0 (0.5)	0.7 (0.3)
25 mg/kg itraconazole	71	69	0.2 (0.2)	8 (4)	2 (2)
Vehicle	2	8	NA ^e	NA	NA

^a All percentages are compared to untreated controls as described in Materials and Methods. All treatments other than vehicle controls were statistically superior to untreated controls (*P* < 0.001).

^b Values are means (standard deviations [SD]); samples taken 1-day posttreatment.

^c Statistically superior to the 25-mg/kg itraconazole group (*P* < 0.05).

^d Below level of detection.

^e NA, not applicable.

FIG 3 Clinical appearance after once-daily versus once-weekly treatment in a guinea pig model of dermatophytosis. Representative photographs of infected areas taken on day 13 of study are shown. Once daily indicates 10 mg/kg antifungal agent dosed by oral gavage for 13 days, and once weekly indicates 70 mg/kg antifungal agent dosed by oral gavage on days 1 and 8. Animals given vehicle control were dosed with 20% Cremophor EL by oral gavage once daily for 13 days. Specifics of the model are described in Materials and Methods.

days are shown in Table 2. The samples were collected 1 day after the last doses were administered and therefore represent the minimum concentration of drug in serum (C_{min}) following the once-daily dose regimen. All VT-1161 levels (0.8 to 40 $\mu\text{g/ml}$ or $\mu\text{g/g}$) were at or above the MIC of the pathogen used in this model (0.5 $\mu\text{g/ml}$ for *T. mentagrophytes* ATCC 24953; Table 1). The VT-1161 plasma levels were very similar to levels at equivalent doses determined in the PK study 24 h after a single dose (Fig. 2).

Efficacy of once-daily versus once-weekly VT-1161 in a guinea pig model of dermatophytosis. Given its long half-life, VT-1161 was evaluated in a subsequent study using two different dosing regimens, either 10 mg/kg once daily or 70 mg/kg once weekly (Fig. 3

and Table 3). The model was slightly modified from that previously employed, as the treatment phase was extended from 9 to 13 days to accommodate the once-weekly regimen (with once-weekly dosing on days 1 and 8). In this study, itraconazole and terbinafine were used as positive controls, and vehicle-treated or untreated guinea pigs served as negative controls. As was seen in the first two studies, all treatment groups were significantly superior to the untreated control groups in regard to the clinical and mycological endpoints ($P < 0.001$; Table 3). The efficacy profile observed with itraconazole and terbinafine when dosed once weekly is consistent with their reported clinical efficacies when dosed in a noncontinuous manner (25, 26). For a visual indication of the severity of infection and the degree of

TABLE 3 Efficacy of once-daily versus once-weekly VT-1161 for guinea pig dermatophytosis

Treatment	Efficacy (%) ^a		Compound level ^b		
	Clinical	Mycological	Plasma (μg/ml)	Skin (μg/g)	Hair (μg/g)
VT-1161 QD ^c	68	97	1.8 (0.3)	27 (5)	7 (3)
VT-1161 QW ^d	87 ^e	94	1.3 (0.3)	24 (6)	10 (10)
Itraconazole QD	82	97	0.12 (0.05)	0.8 (0.2)	12 (8)
Itraconazole QW	62	94	<0.02 ^f	0.3 (0.1)	10 (6)
Terbinafine QD	86	99	<0.02 ^f	0.11 (0.04)	7 (3)
Terbinafine QW	84	96	<0.02 ^f	0.07 (0.02)	9 (3)
Vehicle	4.1	4.3	NA ^g	NA	NA

^a All percentages are compared to untreated controls as described in Materials and Methods. All treatments other than vehicle controls were statistically superior to untreated controls ($P < 0.001$).

^b Values are means (SD); samples taken 1-day posttreatment.

^c QD, 10 mg/kg once daily.

^d QW, 70 mg/kg once weekly on days 1 and 8.

^e Statistically superior to itraconazole QW ($P < 0.05$).

^f Below level of detection.

^g NA, not applicable.

antifungal effect, Fig. 3 shows the clinical appearance of the infected areas on the day 13 evaluation from this study. Unlike the second study described above, when comparing active treatment groups, there were no statistically significant differences between any two mycological scores. However, there was a statistical difference when comparing the clinical scores of the once-weekly regimen of VT-1161 versus itraconazole (Table 3; $P < 0.05$).

The plasma, skin, and hair drug levels for VT-1161, itraconazole, and terbinafine are shown in Table 3. When comparing the plasma and tissue levels after 10 mg/kg once-daily VT-1161 (Table 3) with the values from the same regimen in the second study (Table 2), the levels were similar. When comparing the data for the 10-mg/kg once-daily itraconazole group (Table 3 versus Table 2), the plasma levels were slightly higher (increasing from below detectable to very low but detectable), and the skin levels were similar. However, there was a much higher concentration of itraconazole recorded in hair in the third study. Overall, the concentrations of itraconazole and terbinafine were similar in this study (Table 3)—very low in the plasma, intermediate in the skin, and highest in the hair.

DISCUSSION

Oral therapy for onychomycosis is generally viewed as superior to topical treatment (27). However, complete cure rates of the most commonly used oral drugs (terbinafine and itraconazole) in randomized controlled trials range from approximately 35% to 50% (10), leaving ample room for improvement in clinical efficacy. In addition to improved efficacy, other key features may be optimized for oral therapies, such as reduced drug-drug interactions (13), fewer systemic side effects (14–16) (particularly liver toxicities [11, 12]), and dosing frequency.

VT-1161 is a novel fungal CYP51 inhibitor which was rationally designed to selectively target the fungal enzyme rather than human CYP counterparts while maintaining high potency for the fungal target (20). The potency of VT-1161 in inhibiting fungal CYP51 is <1 nM compared to potencies of ≥ 100 μM in its inhibition of critical human CYPs (21). As was previously noted for a single strain of *Trichophyton rubrum* (20), we report here that VT-1161 had potent intrinsic antifungal activity against clinical

isolates of dermatophytes that cause human disease. Although testing against a larger panel of isolates will be required to fully characterize the *in vitro* activity of VT-1161 against dermatophytes, these data against a small number of isolates are encouraging. Furthermore, single oral doses in the guinea pig led to plasma levels at or above these MIC values for at least 48 h. Thus, it was hypothesized that VT-1161 would show significant clinical and mycological efficacies in a guinea pig model of dermatophytosis if dosed orally once daily. In studies examining once-daily dosing regimens, oral VT-1161 was indeed highly efficacious in suppressing mycological growth and improving the clinical signs of infection. Specifically, in the second study, VT-1161 showed clinical and mycological efficacies that were indistinguishable between its various doses, suggesting that even lower doses may be equally efficacious.

In the second study, the plasma, skin, and hair tissue concentrations of VT-1161 were approximately dose dependent, and all concentrations in all the tissues tested (0.8 to 40 μg/ml or μg/g) were above the MIC of VT-1161 for the *T. mentagrophytes* isolate used in the model (0.5 μg/ml). These data demonstrate that VT-1161 distributed well from plasma into tissues such as skin and hair. In fact, VT-1161 levels were 3-fold to 10-fold higher in the skin and about 2-fold higher in the hair than in the plasma.

Given the long half-life of VT-1161, we hypothesized that it may be administered less frequently than once daily and still maintain efficacy. Therefore, a study was designed to compare once-daily versus once-weekly dosing while approximately maintaining the total amount of drug delivered. All measurements (clinical and mycological evaluations and tissue concentrations) were equivalent between the once-daily and once-weekly VT-1161 regimens. Specifically, this study directly demonstrated that concentrations in plasma, skin, and hair were very similar when the similar total amount of drug was dosed once daily or once weekly. Thus, to first approximation, the long half-life of VT-1161 measured in plasma also occurs in skin and hair tissue, which likely contributed to the efficacy observed when dosing once weekly.

Unlike invasive fungal infections (28–30), the pharmacokinetic/pharmacodynamic (PK/PD) relationship for superficial dermatophyte infections is less well understood. Drug concentrations in the infected tissue (e.g., skin for tinea pedis and nail plate/bed for onychomycosis) are likely important components of a PK/PD relationship, and the literature is replete with measurements of drug concentrations in such tissues in animal models and clinical studies (24, 31, 32). However, which PK parameter (e.g., maximum concentration of drug in serum [C_{max}], C_{min} , area under the concentration-time curve [AUC]) best predicts efficacy and whether free or total drug concentrations should be considered are unknown factors. In the studies presented here, the total drug levels in skin and hair were at or above the MIC in all measurements for each active treatment. In contrast, in four of the six treatment groups in which animals were administered itraconazole or terbinafine, plasma levels were undetectable. Thus, these data suggest that in this model, drug concentrations in skin and hair are a more important parameter to consider in predicting efficacy than are plasma concentrations.

In the absence of a more definitive understanding of dermatophytosis PK/PD, it is clear that VT-1161 had high and sustained exposures not only in plasma but also in key tissues such as skin and hair. In a phase 1 clinical study, we measured VT-1161 levels

in human skin and nail tissues and found the levels in each of these tissue types equivalent to or higher than plasma levels (T. Degenhardt and R. J. Schotzinger, unpublished data). Therefore, VT-1161 is predicted to have significant efficacy in treating dermatophyte infections such as tinea pedis and onychomycosis, in humans. We have in fact demonstrated such “proof-of-concept” efficacy in an ongoing phase 2a clinical study of interdigital tinea pedis (T. Degenhardt, S. R. Brand, and R. J. Schotzinger, unpublished data). Based on the potential to address the efficacy, safety, and dosing frequency challenges associated with current onychomycosis therapy, VT-1161 warrants continued investigation for the treatment of this common and problematic infection.

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