

Luliconazole for the Treatment of Interdigital Tinea Pedis: A Double-blind, Vehicle-Controlled Study

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Tinea pedis (TP) typically is treated with topical antifungal agents. Luliconazole, a novel imidazole drug, is shown to be as or more effective in vitro and in vivo than bifonazole, terbinafine, and lanocanazole. Two treatment durations with luliconazole cream 1% were evaluated for treatment of TP. Participants with interdigital TP were randomized (N= 147) and treated with either luliconazole or its vehicle for either 2 or 4 weeks. The primary efficacy end point was the proportion of participants achieving complete clearance 2 weeks following completion of treatment. In the 2-week active treatment group, complete clearance was achieved in 26.8% (11/41) of participants versus 9.1% (2/22) in the 2-week vehicle group at 2-weeks posttreatment. In the 4-week active treatment group, 45.7% (16/35) achieved complete clearance versus 10.0% (2/20) in the 4-week vehicle group at 2-weeks posttreatment. Twenty-three adverse events (AEs) were reported; most were mild (56.5% [13/23]) to moderate (26.1% [6/23]) in severity. All reported

AEs were determined to be unrelated (78.3% [18/23]) or unlikely related (21.7% [5/23]) to the study medication. The results of this study indicate that luliconazole cream 1% applied once daily for either 2 or 4 weeks is safe and effective for treatment of TP. More importantly, the antifungal effects of luliconazole persist for several weeks, resulting in increased rates of mycological cure.

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Tinea pedis (TP) is a fungal infection of the skin that primarily affects the interdigital areas of the feet, manifesting with pruritus, cracking, maceration, scaling, and erythema.¹⁻³ It is likely to be more severe in immunocompromised patients⁴ and can potentially lead to secondary bacterial infections and cellulitis in individuals with diabetes mellitus.⁵

The fungal pathogens most frequently associated with TP are *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and occasionally *Epidermophyton floccosum*.⁶ Topical antifungal preparations are a mainstay of treatment of TP; however, 1 to 4 weeks of therapy generally are required and recurrence is common.¹ After successful topical or systemic therapy, recurrence occurs in up to 70% of patients.⁷

Luliconazole is a novel imidazole drug with in vitro antifungal activity against dermatophytes and *Candida albicans*.⁸ The effectiveness of luliconazole is equal to or exceeds that of other antifungal agents, including bifonazole and terbinafine, based on its minimum inhibitory concentration.^{9,10} In an animal model of dermatophytosis, luliconazole was as effective as terbinafine and superior to lanocanazole.¹¹ Luliconazole cream 1% has been approved in Japan for treatment of tinea infections since 2005. Although there is a large body of safety and efficacy information for a number of luliconazole formulations among the

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Japanese population, to our knowledge there have been no reported efficacy and safety studies of luliconazole in the US population for this indication.

This US-based study evaluated the safety and efficacy of 2 treatment durations of luliconazole cream 1% for interdigital TP.

Methods

Participants—The study included males and females aged 12 years or older who had been diagnosed with interdigital TP (ie, athlete's foot) on 1 or both feet with clinical signs of erythema and scaling that were rated at least moderate and pruritus that was rated at least mild according to physician global assessment (PGA) scores. Enrollment was based on a clinical diagnosis of TP, which was confirmed by the presence of fungal hyphae on microscopic potassium hydroxide (KOH) wet mount. Eligibility to continue treatment after enrollment was confirmed by positive culture and identification of dermatophyte species by a central laboratory using skin samples taken from the site of the TP infection. If the culture was determined to be negative for dermatophytes after the participant was enrolled, he/she was deemed a delayed exclusion and was not included in the efficacy assessments but remained in the safety population.

Key exclusion criteria included moccasin-type TP, concurrent onychomycosis, severe dermatophytosis, or a concurrent bacterial skin infection on the evaluated foot. Participants who were immunocompromised or were hypersensitive to imidazole compounds or any component of the study medication also were excluded, as well as women who were pregnant, breastfeeding, or planning to become pregnant. A minimum washout period of 30 days was required for topical antifungal agents and topical or systemic corticosteroids, 8 months for systemic terbinafine, 8 weeks for all other systemic antifungal agents, and 7 days for all other topical medications. Participants were instructed not to apply any other creams, lotions, powders, or ointments to the treatment area throughout the duration of the study.

Study Drug—A luliconazole—(-)-(E)-[(4R)-4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene] (1H-imidazol-1-yl) acetonitrile (C₁₄H₉Cl₂N₃S₂)—1% cream formulation was utilized. The control vehicle consisted of all excipients except luliconazole.

Study Design and Treatment—Participants were randomly assigned to receive treatment with luliconazole cream 1% for 2 or 4 weeks or vehicle for 2 or 4 weeks in a 2:2:1:1 ratio. Enrollment continued until a minimum of 120 eligible participants were enrolled at 5 study centers. Participants were instructed to thoroughly clean and dry the affected area and apply approximately 1 g of the assigned treatment

once daily in the evening to the treatment site and approximately 2.5 cm (1.0 in) of the surrounding healthy skin. The initial application was administered by participants at the clinic under staff supervision, while subsequent applications were made by the participants alone.

Following the baseline visit, participants in both 2-week treatment groups were evaluated at the end of treatment as well as at 2- and 4-weeks posttreatment. Participants in both 4-week treatment groups were evaluated at week 2 and at the end of treatment as well as at 2- and 4-weeks posttreatment (Figure 1).

Extent of Drug Exposure—The mean number of applications in the 2- and 4-week active treatment groups was 14.2 and 27.1, respectively; the mean number of applications in the corresponding vehicle groups was 14.4 and 27.6, respectively. Only 2 participants in the 4-week active treatment group and 1 participant in the 4-week vehicle group were not compliant with the dosing regimen.

Efficacy Assessment—The primary end point was the proportion of participants in both 2- and 4-week groups who achieved complete clearance 2 weeks following completion of treatment (28 and 42 days, respectively). Complete clearance was defined as achieving both clinical cure (score of 0 on a 4-point static PGA scale)(Table 1) and mycological cure (negative microscopic KOH examination and fungal cultures). The PGA allowed minimal residual erythema.

Secondary end points included the proportion of participants for the following assessments: effective treatment (defined as a PGA score of 0 to 1 and negative KOH and fungal culture), clinical cure, mycological cure, and complete clearance, all at the end of treatment as well as at 2- and 4-weeks posttreatment. Additionally, fungal isolates were collected from all enrolled participants for identification of

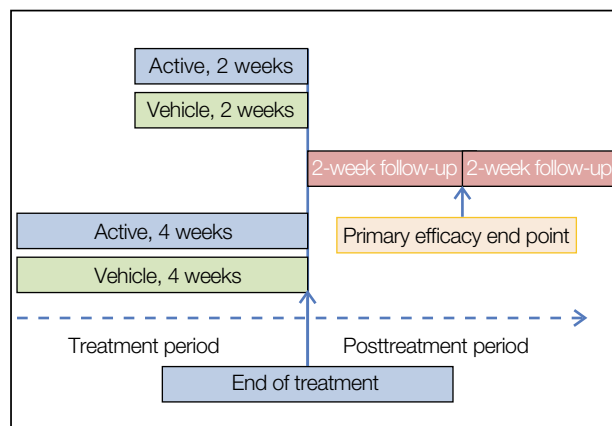


Figure 1. Study design.

Table 1.

Physician Global Assessment Scale

Score	Grade	Description
0	Clear	No evidence of scaling, pruritus, and erythema (residual erythema could be present)
1	Mild	Interdigital erythema and scaling were present between some toes but were mild; minimal pruritus could be present
2	Moderate	Definite interdigital erythema and scaling were present between most toes accompanied by marked pruritus
3	Severe	Significant erythema, scaling, and pruritus were present between most toes

dermatophyte species using standard mycology laboratory techniques.

Safety Assessment—Safety assessment included standard hematology, serum chemistry, and urinalysis performed by a central laboratory at baseline and on the last day of treatment. Participants were encouraged to report possible adverse events (AEs) to the investigators throughout the study and were questioned about possible AEs at each visit to the clinic. Safety assessment also included evaluation of vital signs, prior and concomitant medications, and urine pregnancy tests for female participants of childbearing potential. Treatment-emergent AEs were defined as events with onset on or after the date of treatment initiation and were classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA)(version 12.0).

Statistical Analyses—Primary and secondary efficacy end points were summarized by treatment group with frequency counts and percentages. No *P* values were reported. Additionally, descriptive statistics were presented for PGA and for individual signs of TP at baseline and at each visit to the clinic up to 4-weeks posttreatment. Demographic and baseline

characteristics for each treatment group were summarized using descriptive statistics.

All efficacy analyses were based on the modified intention-to-treat population, which was defined as those participants who were randomized, received treatment with a study medication, and had positive baseline KOH examinations and fungal cultures. The last-observation-carried-forward method was used to impute missing data, such as missed clinic visits. Causal fungal organisms also were summarized with frequency counts and percentages. Additional analysis was conducted at day 42 (4 weeks after completion of the 2-week treatment and 2 weeks after completion of the 4-week treatment) to assess the time course of complete clearance using Kaplan-Meier plots. All statistical analyses were performed using statistical analysis software.

Study Ethics—This study was conducted in compliance with US Food and Drug Administration regulations, the ethical principles set forth by the World Medical Association in the Declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol, informed consent, and other study-related documents were approved by an institutional review board prior to use in the study. Each enrolled participant provided informed consent prior to participating in any study-related activities.

Results

A total of 147 participants were randomized to the 2-week (n=50) and 4-week (n=49) active treatment groups as well as the 2-week (n=24) and 4-week (n=24) vehicle groups. Twenty-nine participants were excluded from efficacy analysis due to a negative mycological culture (delayed exclusions), leaving a modified intention-to-treat population of 118 participants. The delayed exclusion implied that participants could be enrolled without awaiting fungal culture results. The safety population included participants who applied at least 1 dose of study medication (N=146); 1 participant was excluded from the safety population due to the lack of a post-baseline assessment. Participant disposition is shown in Figure 2.

Demographics—The mean age of enrolled participants was 37.3 years (age range, 12–76 years) and they were predominantly male (76.7% [112/146]), non-Hispanic/Latino (78.0% [114/146]), and white (75.3% [110/146]) or black (20.5% [30/146]). Participant demographic characteristics were similar between all 4 treatment groups (Table 2). Based on the PGA scores at baseline, the majority of enrolled participants displayed symptoms of moderate severity (79.4% [116/146]), consisting of moderate erythema

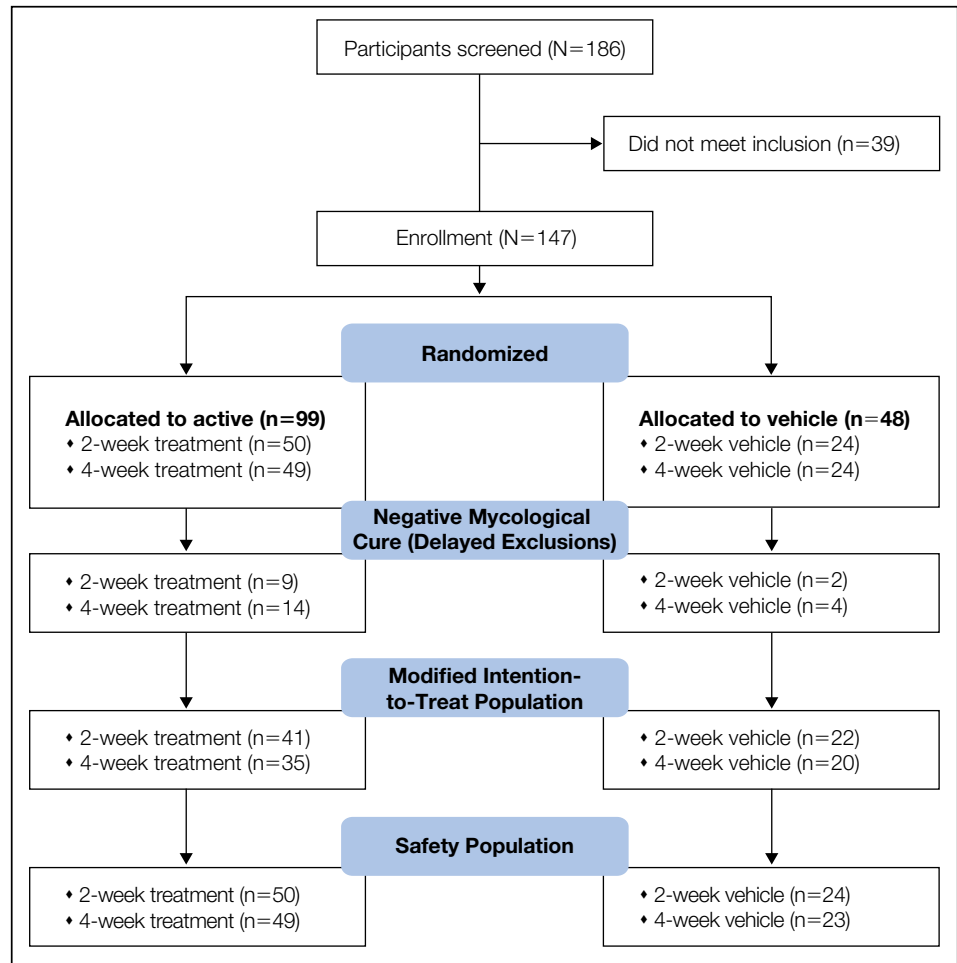


Figure 2. Participant disposition.

Table 2.

Participant Demographics and Baseline Characteristics (Safety Population; N=146)

Demographics	Active Treatment		Vehicle	
	2 Weeks (n=50)	4 Weeks (n=49)	2 Weeks (n=24)	4 Weeks (n=23)
Median age (range), y	36 (15–69)	39 (12–60)	37 (16–76)	38 (18–64)
Gender, n (%)				
Male	41 (82.0)	34 (69.4)	20 (83.3)	17 (73.9)
Female	9 (18.0)	15 (30.6)	4 (16.7)	6 (26.1)
Ethnicity, n (%)				
Non-Hispanic	37 (74.0)	39 (79.6)	20 (83.3)	18 (78.3)
Hispanic	13 (26.0)	10 (20.4)	4 (16.7)	5 (21.7)
Race, n (%)				
White	37 (74.0)	38 (77.6)	18 (75.0)	17 (73.9)
Black	9 (18.0)	11 (22.4)	4 (16.7)	6 (26.1)
Asian	1 (2.0)	0 (0)	1 (4.2)	0 (0)
Other	3 (6.0)	0 (0)	1 (4.2)	0 (0)

(88.3% [129/146]) and scaling (71.2% [104/146]) and mild to moderate pruritus (78.7% [115/146]).

Mycology—*Trichophyton rubrum* was isolated in 82.9% (34/41) of participants in the 2-week active treatment group and 85.7% (30/35) of participants in the 4-week active treatment group. *Trichophyton mentagrophytes* was seen in 7.3% (3/41) of participants and 5.7% (2/35) of participants in the 2- and 4-week active treatment groups, respectively, whereas *E floccosum* was found in 7.3% (3/41) of participants and 8.6% (3/35) of participants in both active treatment groups, respectively. One participant in the 2-week active treatment group had an infection involving both *T rubrum* and *T mentagrophytes*.

Primary End Point—The primary efficacy end point, defined as complete clearance (both clinical and mycological cure), was measured at 2 weeks posttreatment in the 2- and 4-week active treatment groups. In the 2-week active treatment group, complete clearance was achieved in 26.8% (11/41) of participants versus 9.1% (2/22) in the 2-week vehicle

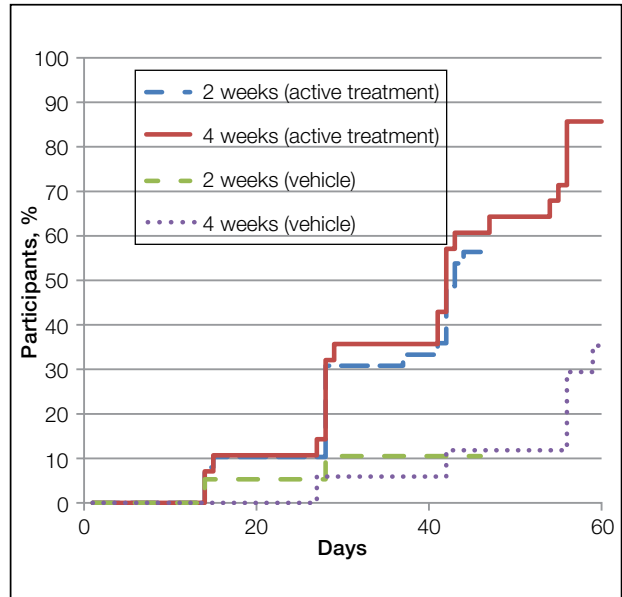


Figure 3. Kaplan-Meier plots for complete clearance (modified intention-to-treat population [N=118]).

Table 3.

Secondary Efficacy End Points (Modified Intention-to-Treat Population; N=118)^a

Secondary Efficacy End Point	Active Treatment		Vehicle	
	2 Weeks (n=41)	4 Weeks (n=35)	2 Weeks (n=22)	4 Weeks (n=20)
End of treatment, n (%)				
Clinical cure	4 (9.8)	8 (22.9)	1 (4.5)	1 (5.0)
Mycological cure	24 (58.5)	27 (77.1)	10 (45.5)	8 (40.0)
Effective treatment	13 (31.7)	22 (62.9)	3 (13.6)	4 (20)
2-weeks posttreatment, n (%)				
Clinical cure	12 (29.3)	16 (45.7)	2 (9.1)	3 (15.0)
Mycological cure	32 (78.0)	31 (88.6)	10 (45.5)	7 (35.0)
Effective treatment	21 (51.2)	25 (71.4)	6 (27.3)	4 (20.0)
4-weeks posttreatment, n (%)				
Clinical cure	23 (56.1)	24 (68.6)	2 (9.1)	5 (25.0)
Mycological cure	34 (82.9)	32 (91.4)	6 (27.3)	8 (40.0)
Effective treatment	26 (63.4)	29 (82.9)	4 (18.2)	7 (35.0)
Complete clearance	22 (53.7)	22 (62.9)	1 (4.5)	5 (25.0)

Abbreviations: TP, tinea pedis; PGA, physician grading assessment; KOH, potassium hydroxide.

^aClinical cure defined as the absence of the signs or symptoms of TP (score of 0 [clear] on the static PGA scale). Mycological cure defined as negative KOH examination and fungal culture. Effective treatment defined as a PGA score of 0 to 1 (mild erythema and/or scaling and minimal pruritus) and negative KOH and fungal culture. Complete clearance defined as achieving both clinical and mycological cure.

group. In the 4-week active treatment group, 45.7% (16/35) of participants achieved complete clearance versus 10.0% (2/20) in the 4-week vehicle group.

Figure 3 provides a graphic display of Kaplan-Meier plots showing the course of time for achieving complete clearance. In participants who achieved complete clearance, the time at which complete clearance initially was achieved was used as their time to complete clearance. Participants who never achieved complete clearance in this study were treated as censored observations. An analysis of response curve conducted in all groups through 42-days postbaseline showed that the response curves for the 2-week and 4-week active treatments were overlapping and that the course of time for resolution of TP was similar for both active treatment groups (Figure 3).

Secondary efficacy end points for all treatment groups are presented in Table 3. As expected, response to treatment was low at the early time points and increased over time. In the 2-week active treatment group, 58.5% (24/41) of participants demonstrated mycological cure at end of treatment, which increased to 78.0% (32/41) at 2-weeks posttreatment and 82.9% (34/41) at 4-weeks posttreatment (day 42). Likewise, in the 4-week active treatment group, 77.1% (27/35) of participants demonstrated mycological cure at end of treatment, which increased to 88.6% (31/35) at 2-weeks posttreatment and 91.4% (32/35) at 4-weeks posttreatment (day 56)(Table 3).

Safety—None of the participants withdrew from the study because of an AE. Of the 23 AEs reported across all 4 treatment groups (N=146), the majority were mild in severity (56.5% [13/23]); some were moderate (26.1% [6/23]) or severe (17.4% [4/23]) (Table 4). All reported AEs were determined to be unrelated (78.3% [18/23]) or unlikely related (21.7% [5/23]) to the study medication. The most common AEs reported by participants in the active treatment groups included headache (3% [3/99]), injury (2% [2/99]), and cough (2% [2/99]). Reported AEs among participants in the 2- and 4-week vehicle groups included nasopharyngitis, bacterial vaginitis, and back injury (2% [1/47] each); these AEs were mild in severity and were found to be unrelated to the study drug. Severe AEs included increased levels of alanine aminotransferase, aspartate aminotransferase, blood creatine phosphokinase, and blood lactate dehydrogenase in 1 patient in the 4-week active treatment group. One participant in the 4-week active treatment group reported asthenia and chest pain; both of these events were considered moderate in severity and were found to be unrelated to the study drug. In both instances, the events resolved and the participant continued treatment without interruption.

Comment

Consistent with results from in vitro studies and animal models of dermatophytosis, mycological results in

Table 4.

Summary of Treatment-Emergent AEs (Safety Population; N=146)

	Active Treatment		Vehicle	
	2 Weeks (n=50)	4 Weeks (n=49)	2 Weeks (n=24)	4 Weeks (n=23)
Participants reporting ≥1 AE, n (%) ^a	6 (12.0)	7 (14.3)	1 (4.2)	2 (8.7)
No. of AEs reported	6	14	1	2
Serious AEs, n (%) ^b	0 (0)	2 (14.3)	0 (0)	0 (0)
Severity, n (%) ^b				
Mild	4 (66.7)	6 (42.9)	1 (100)	2 (100)
Moderate	2 (33.3)	4 (28.6)	0 (0)	0 (0)
Severe	0 (0)	4 (28.6)	0 (0)	0 (0)

Abbreviation: AE, adverse event.

^aBased on number of participants.

^bBased on number of events.

this study also showed luliconazole to be highly effective against dermatophytes in the clinical setting. As expected,⁶ *T rubrum* was detected in baseline tissue samples in the majority of participants (82.9%) with TP. The results of this study demonstrated the efficacy of luliconazole against this fungal pathogen.

The expected outcome for antifungal drugs is clinical cure, which ultimately depends on how effectively the drug eradicates the fungus (ie, mycological cure). The proportion of participants who demonstrated mycological cure at the end of treatment in the 2-week active treatment group was higher than in the 2-week vehicle group (58.5% vs 45.5%) but increased when measured at 2- (78.0% vs 45.5%) and 4-weeks posttreatment (82.9% vs 27.3%) despite no additional treatments. Moreover, the clinical cure rates for the 2-week active treatment group at 2- and 4-weeks posttreatment were nearly 3-fold (29.3%) and 6-fold (56.1%) those observed at end of treatment (9.8%), indicating that clinical cure rates increased with time during posttreatment follow-up.

Compared to the end of treatment, the proportion of participants with clinical cure in the 2- and 4-week vehicle groups remained approximately the same at 2- and 4-weeks posttreatment whereas the proportion of participants with mycological cure dropped by 40% in the 2-week vehicle group or remained the same in the 4-week vehicle group. The substantial decrease over time suggested that the participant response to the vehicle observed earlier in the treatment period is nonspecific and unsustainable, whereas luliconazole-mediated fungal killing and the clinical clearance of the TP continues for weeks after the final topical application of the drug. Such vehicle responses are not uncommon with topical antifungal agents, suggesting that true therapeutic benefits only follow fungal eradication.

Complete clearance (primary efficacy end point) is a composite cure defined by both clinical and mycological cure. Extending the treatment duration from 2 to 4 weeks increased the proportion of participants with complete clearance at both 2- and 4-weeks posttreatment (26.8% and 45.7%, respectively) in the active treatment group but had little effect on the vehicle groups. Although the proportion of participants who demonstrated complete clearance continued to rise 4-weeks posttreatment in the 2- and 4-week active treatment groups versus the 2- and 4-week vehicle groups (2 weeks, 53.7% vs 4.5%; 4 weeks, 62.9% vs 25.0%), the difference in cure rates between the 2 active treatment groups was small at this end point, suggesting a posttreatment duration reduced the differences.

A post hoc analysis of primary efficacy using only participants who had no erythema (versus residual

erythema) in all 4 treatment groups showed little numeric difference in comparison with the original analysis (results not shown). These results suggested that inclusion or exclusion of residual erythema in the assessment of clinical cure does not numerically affect the efficacy rates.

Doubling the duration of treatment with luliconazole cream 1% from 2 to 4 weeks only modestly increased mycological and/or clinical cure rates when measured at the end of treatment, suggesting that the potent fungicidal activity of luliconazole is rapid and does not require prolonged treatment and indicating that clinical cure is secondary to mycological cure. Therefore, the posttreatment time period appeared to play a more critical role than the actual length of treatment in the context of this study. In the 4-week active treatment group, the mycological cure rates steadily increased from 77.1% to 88.6% to 91.4% at end of treatment and 2- and 4-weeks posttreatment, respectively. Compared to the results observed in the 2-week active treatment group (58.5%, 78.0%, and 82.9%, respectively), these findings are strong evidence for limiting treatment to 2 weeks. These findings are comparable to results of a prior study conducted in Japan in patients with TP that reported mycological cure rates of 76% and 88% 2 weeks after application of luliconazole cream 1% once daily for 2 weeks.¹² The duration of treatment also is favorable compared to other topical regimens used for treatment of TP, such as 2 to 4 weeks of twice-daily treatment with econazole, up to 4 weeks of twice-daily treatment with sertaconazole, 1 to 2 weeks of twice-daily treatment with terbinafine, and 4 weeks of once-daily application of naftifine.¹³ Given the several years of clinical experience using luliconazole for treatment of TP in Japan, it is likely that luliconazole development in the United States will provide new treatment options for patients.

The safety and tolerability profile of luliconazole cream 1% was remarkably favorable in that no treatment-related AEs were reported, including application-site reactions and systemic events.

Conclusion

The results of this study indicate that luliconazole cream 1% is safe, well tolerated, and effective for the treatment of TP. When applied once daily for either 2 or 4 weeks, the antifungal effects of luliconazole persisted for several weeks posttreatment, resulting in increased rates of mycological cure and corresponding clinical cure as time progressed. The clinical response (complete clearance) at day 42 for participants in the 2-week treatment group was similar to that observed at day 42 for the 4-week treatment group. Given these results, a 2-week treatment period appears to be

sufficient in providing a high degree of efficacy and should be further evaluated in larger phase 3 studies.

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