ORIGINAL ARTICLE

Efficacy, safety and tolerability of topical terbinafine nail solution in patients with mild-to-moderate toenail onychomycosis: results from three randomized studies using double-blind vehicle-controlled and open-label active-controlled designs

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Abstract

Background Terbinafine nail solution (TNS) was developed for the treatment of onychomycosis.

Objective To assess the efficacy of TNS vs. vehicle and amorolfine 5% nail lacquer.

Methods Subjects with mild-to-moderate toe onychomycosis (25% to ≤75% nail-involvement, matrix uninvolved) were randomized to receive either TNS or vehicle in two double-blind studies, and to TNS or amorolfine in an active-controlled, open-label study. Primary endpoint was complete cure (no residual clinical involvement and negative mycology) at week 52. Secondary endpoints were mycological cure (negative mycology defined as negative KOH microscopy and negative culture) and clinical effectiveness (≤10% residual-involvement and negative mycology) at week 52.

Results Complete cure was not different between TNS vs. vehicle and amorolfine. Mycological cure was higher with TNS vs. vehicle, as was clinical effectiveness with TNS vs. vehicle, and TNS and amorolfine were not different for secondary efficacy endpoints. Patients achieving mycological cure had a better clinical outcome, and efficacy was improved in subjects with milder disease. *Post hoc* analysis suggests that nail thickness is an important prognostic factor. Moreover, mycological cure may require 6 months of treatment regimen while complete cure and clinical effectiveness may be achievable only after 10 months. A simulation study suggests that longer treatment duration would have resulted in higher complete cure with TNS vs. vehicle. Study treatments were well-tolerated.

Conclusion Primary efficacy objectives were not met in the studies reported herein. Possible reasons for failure to achieve significant outcomes include insufficient length of treatment; stringency of primary endpoint and severity of nail involvement of study population.

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Conflict of interest

H.C. Korting has previously collaborated with Novartis in the development of topicals containing terbinafine, and with Galderma concerning amorolfin-containing preparations. Drs'. P. Mayser, R. Shouey, A. Gupta and B.

Sigurgeirsson have no conflict of interests. S. Hugot, M. Notter, K. Thangavelu, A. Parneix-Spake and J. Nyirady are employees of Novartis. Drs' B.E. Elewski, P. Rich and M. Ling have received research grant fund from Novartis for the performing of the study. Dr B. Damaj is an employee of NexMed (USA), Inc. Dr D. Baker was a principal investigator at one of the research sites. Dr M. Ghannoum has accepted as a consultant for Novartis Pharmaceuticals.

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Introduction

Onychomycosis is the most common cause of nail dystrophy, affecting 12–13% of the general population,[1–7] and 25% of the geriatric and diabetic population.[6,8,9] The disease can be painful or cause functional disability, psychosocial problems and compromised quality of life.[10–12]

Topical treatments are generally reserved for mild cases of onychomycosis as they are less effective than systemic oral therapy due to reasons including poor penetration, less depot effect and less depot area.[13] However, systemic therapy is not recommended in some patients due to the risk of possible drug–drug interactions and patient co-morbidities.[14,15] Because of the slow growth rate of toenails, treatment of toe onychomycosis is more challenging than finger onychomycosis and it may take up to 18 months of therapy to achieve clearance.[16–20] Although topical agents like amorolfine 5% (marketed in Europe) and ciclopirox 8% (available in Europe and US) formulated as lacquers have improved drug delivery to nails,[21] cure rates are lower than with systemic therapy and re-infection or relapse often occurs, as is the case with oral anti-fungal therapy.[14,16,22,23]

Terbinafine, a synthetic allylamine is a well-established broad-spectrum anti-fungal drug,[24] with unique clinical efficacy combined with good tolerability.[17,25] Based on the reservoir effect observed with a film-forming solution of terbinafine 1%[26,27] (allowing for a single-application treatment of interdigital tinea pedis), a nail solution [topical terbinafine HCl nail solution (TNS)] was developed. This formulation demonstrated mycological and clinical efficacy in *in vitro*[28] models of onychomycosis and was superior to ciclopirox 8% nail lacquer in a Phase II study.[29] This article presents results from three large clinical studies [two vehicle-controlled (2301 & 2302) and one active comparator-controlled study (2303)] which assessed efficacy and safety of TNS used for 24 weeks and 48 weeks in patients with mild-to-moderate toenail onychomycosis.

Methods

Study design

In the vehicle-controlled studies, subjects received either TNS or vehicle for 24 weeks or 48 weeks followed by a treatment free period of 28 weeks or 4 weeks respectively. In the active comparator-controlled study, subjects received either TNS or amorolfine 5% nail lacquer for 48 weeks followed by a treatment free period of 4 weeks. The total duration of each study was 52 weeks. Subjects were randomized using a validated automated system in equal ratios.

The studies were conducted in accordance with the ethical principles specified in the Declaration of Helsinki and in compliance with the requirements of local regulatory committees and all subjects provided written informed consent.

Subjects

Subjects aged 12–75 years with mild-to-moderate toe onychomycosis of the great toenail due to dermatophytes were included. Mild-to-moderate toe onychomycosis was defined as a toenail involvement of ≥25% to ≤75% without spikes and without matrix (lunula) involvement, and nail infection was confirmed by positive KOH microscopy and culture of a dermatophyte. The subjects who had nail abnormalities, obscuring appearance of infection-free normal nail (including traumatic or onychogryphotic nail) or in whom the target toenail had <2 mm unaffected nail plate length beyond the proximal fold were excluded. Also excluded were those with severe plantar tinea pedis requiring systemic therapy, mixed infections (dermatophyte and non-dermatophyte), dermatophytoma (thick masses of fungal hyphae between the nail plate and nail bed),[30] those receiving systemic or topical anti-fungal therapy within 6 months or 3 months, respectively, and those who used any commercial topical nail medication within 1 month. Subjects with severe diabetic foot neuropathy, malignancy, and sensitivity to the study medication were also excluded.

Treatment

Terbinafine nail solution or vehicle were supplied in identical packaging and were to be applied daily to all affected toenails with no surgical debridement, chemical avulsion, excessive grinding or filing of diseased nails. Amorolfine 5% nail lacquer was supplied as commercially available and was used as per label, twice weekly and with filling of the nails, as described in the package insert.

Efficacy and safety assessments

The primary efficacy measure was the proportion of subjects achieving complete cure (no residual clinical involvement and negative KOH and culture) of the target toenail at week 52. The secondary

efficacy endpoints were rates of mycological cure (negative KOH microscopy and negative culture for dermatophyte), clinical effectiveness (≤10% residual involvement of the target toenail, negative culture and negative KOH microscopy) and clinical cure (no residual involvement of the target toenail) at week 52. In addition, the proportion of subjects achieving a negative culture and ≥50% decrease in per cent involvement of the target toenail was analyzed.

The safety assessments included monitoring and recording of all adverse events until week 52.

Susceptibility testing

Terbinafine susceptibility, expressed as minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC), for all strains isolated at baseline was assessed using the method developed under auspices of the Clinical and Laboratory Standards Institute (CLSI).[31,32]

Statistical analyses

Data from the two vehicle-controlled studies were combined for analysis. The intent-to-treat (ITT) population included all subjects who were randomized and dispensed study drug and the safety population included all subjects who received at least one dose of study drug. For the combined analysis of the efficacy, a normal inverse combination test was performed that combines the one-sided *P*-values, generated for the individual studies by one-sided Fisher's exact tests, using a standard normal test statistic.[33] In the active comparator-controlled study, the efficacy endpoints were compared using a two-sided Cochran–Mantel–Haenszel test at a 5% level of significance. As none of the primary analyses yielded a statistically significant result, the results for the secondary endpoints are descriptive rather than confirmatory. Missing values were imputed using the last observation carry forward (LOCF) approach.

Based on the results from the two vehicle-controlled studies, a chronological dependence was observed in subjects achieving mycological cure to clinical effectiveness to complete cure. This information was used to simulate cure rates for up to 18 months of treatment.

Sample size

Sample sizes for each study were chosen to achieve 90% power to detect a difference in complete cure rates (16% for TNS vs. 2% and 8% for vehicle and amorolfine respectively). Assuming a drop-out rate of 18% and 20% for the vehicle-controlled studies and the active comparator-controlled study respectively, a total of 500 subjects were needed for each vehicle-controlled study and 926 subjects for the active-controlled study.

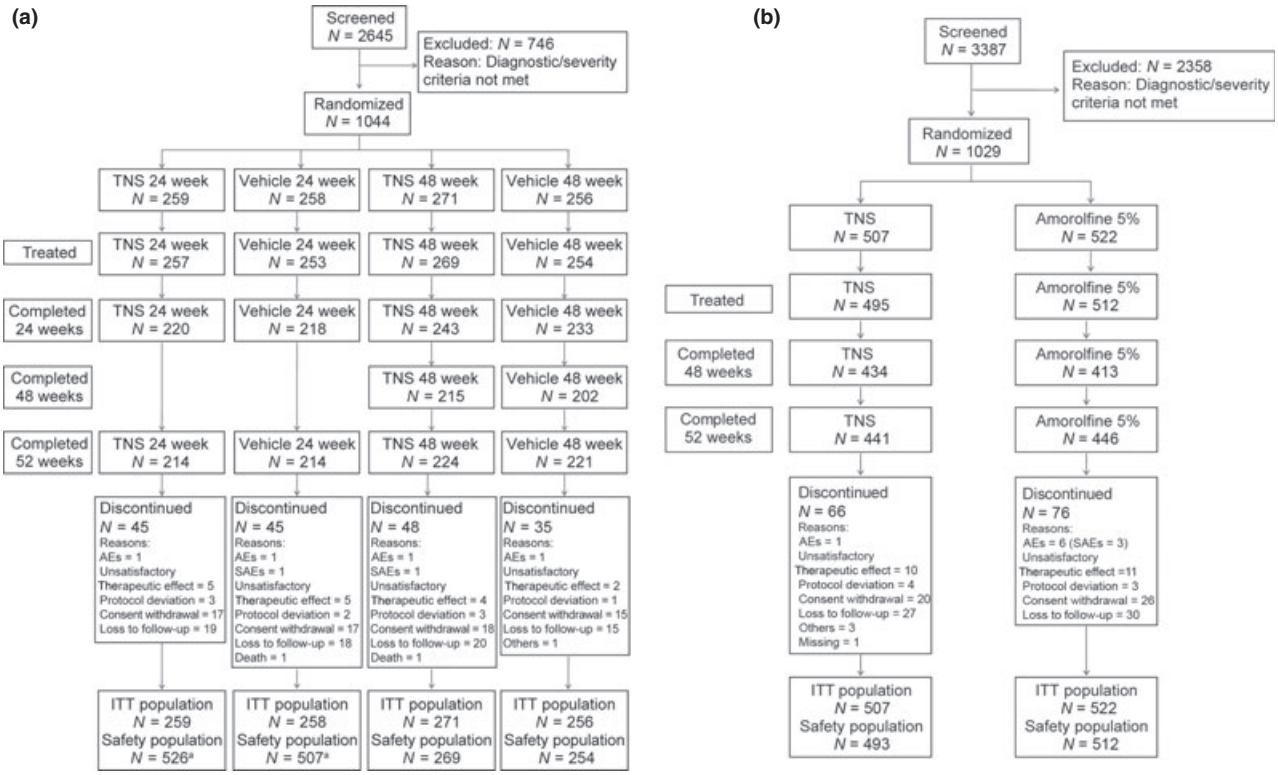

Figure 1 (a) Patient disposition for double-blind vehicle-controlled studies; pooled data. (b) Patient disposition for open-label active-controlled study. [a]The 24 week and 48 week treatment groups were pooled for data collected up to week 28. This included a follow-up period of 4 weeks without treatwent for the 24 week treatment groups.

Results

Subjects

A total of 1044 and 1029 subjects were respectively randomized in the vehicle and active-controlled studies, and 530 and 507 subjects respectively received active TNS treatment (Fig. 1a,b). At baseline, a majority of subjects had >4 affected toenails, approximately 40% of them in all three studies had nail thickness ≥3 mm and the majority (about 55–65%) had >40% nail involvement, indicating a rather severe disease population for treatment with a topical product (Table 1). *T. rubrum* was the affecting dermatophyte in >92% of the cases.

Efficacy

Complete cure The proportion of subjects achieving complete cure was neither significantly different between TNS and vehicle nor between TNS and active comparator amorolfine (Table 2).

Mycological cure A higher proportion of subjects achieved mycological cure with TNS than with vehicle. However, mycological cure was similar in the TNS vs. amorolfine groups (Table 2). Further, the proportion of subjects in TNS and amorolfine groups with a negative KOH microscopy were similar.

Clinical cure Clinical effectiveness was numerically higher with TNS 48 week vs. vehicle group; however, the clinical cure rate was not different between the two groups. Further, both TNS and amorolfine treatment groups were comparable in terms of clinical cure rates and clinical effectiveness (Table 2).

Exploratory analyses Subjects with less severe disease (≤50% nail involvement, ≤2 mm nail thickness and disease duration ≤65 months) achieved complete cure more often than those with more severe disease. The proportion of subjects who achieved negative culture and ≥50% decrease in % involvement of the target toenail was higher with TNS 48-week treatment than with vehicle

Table 1 Baseline demographics and disease characteristics of the subjects

	Vehicle-controlled studies				Active comparator-controlled study	
	24-Week treatment		48-Week treatment		48-Week treatment	
	TNS *n* = 259	Vehicle *n* = 258	TNS *n* = 271	Vehicle *n* = 256	TNS *n* = 507	Amorolfine 5% *n* = 522
Age in years, mean ± SD	53.7 ± 12.86	52.7 ± 12.51	54.0 ± 11.78	53.9 ± 12.09	52.8 ± 12.15	52.6 ± 12.97
Gender, *n* (%)						
Male	200 (77.2)	190 (73.6)	204 (75.3)	194 (75.8)	349 (68.8)	372 (71.3)
Female	59 (22.8)	68 (26.4)	67 (24.7)	62 (24.2)	158 (31.2)	150 (28.7)
KOH microscopy, *n* (%)						
Positive	259 (100)	258 (100)	271 (100)	256 (100)	506 (99.8)	518 (99.2)
Culture for dermatophytes, *n* (%)						
Positive	258 (99.6)	257 (99.6)	269 (99.3)	255 (99.6)	501 (98.8)	513 (98.3)
Dermatophytes species, *n* (%)						
T. rubrum	252 (97.3)	237 (91.9)	255 (94.1)	240 (93.8)	484 (95.5)	488 (93.5)
T. mentagrophytes	5 (1.9)	18 (7.0)	14 (5.2)	14 (5.5)	17 (3.4)	25 (4.8)
Others	1 (0.4)	2 (0.8)	0 (0)	1 (0.4)	6 (1.2)	9 (1.7)
% NI, *n* (%)*						
Mean ± SD	48.9 ± 14.86	47.2 ± 15.32	49.3 ± 14.48	48.4 ± 14.84	51.9 ± 17.13	50.4 ± 16.32
≤40%	114 (44.0)	119 (46.1)	107 (39.5)	108 (42.2)	178 (35.1)	204 (39.1)
>40%	145 (56.0)	139 (53.9)	164 (60.5)	148 (57.8)	329 (64.9)	316 (60.5)
NT, *n* (%)**						
≤2 mm	152 (58.7)	153 (59.3)	160 (59.0)	154 (60.2)	292 (57.6)	306 (58.6)
3 mm	63 (24.3)	62 (24.0)	63 (23.2)	58 (22.7)	125 (24.7)	108 (20.7)
>3 mm	44 (17.0)	43 (16.7)	48 (17.7)	44 (17.2)	89 (17.6)	108 (20.7)
Disease severity, *n* (%)***						
≤2 mm NT and ≤40% NI	77 (29.7)	74 (28.7)	65 (24.0)	72 (28.1)	127 (25.0)	147 (28.2)
>2 mm NT or >40% NI	182 (70.3)	184 (71.3)	206 (76.0)	184 (71.9)	380 (75.0)	374 (71.6)

*In active comparator-controlled study, two patients (0.4%) missing in amorolfine group.

**In active comparator-controlled study, one patient (0.2%) missing in TNS group.

***In active comparator-controlled study, one patient (0.2%) missing in each of the TNS and amorolfine groups.

NI, nail involvement; NT, nail thickness; TNS, terbinafine nail solution.

Table 2 Primary and secondary efficacy variables at the end of the study (week 52) in vehicle-controlled studies and active comparator-controlled study

	Vehicle-controlled studies						Active comparator-controlled study		
	24-Week treatment			48-Week treatment			48-Week treatment		
	TNS *n* = 259	Vehicle *n* = 258	Difference* (95% CI)	TNS *n* = 271	Vehicle *n* = 256	Difference* (95% CI)	TNS *n* = 507	Amorolfine 5% *n* = 522	Difference** (95% CI)
Complete cure rate†, *n* (%)	3 (1.2)	2 (0.8)	0.38 (−1.3, 2.1) *P* = 0.6864	6 (2.2)	0 (0)	2.21 (0.5, 4.0) *P* = 0.0668	6 (1.2)	5 (0.96)	0.23 (−1.03, 1.4) *P* = 0.7302
Mycological cure rate‡, *n* (%)	33 (12.7)	16 (6.2)	6.54 (1.5, 11.6) *P* = 0.0141	51 (18.8)	14 (5.5)	13.35 (7.9, 18.8) *P* < 0.0001	82 (16.2)	82 (15.7)	0.86 (−3.2, 4.9) *P* = 0.6843
Clinical effectiveness§, *n* (%)	6 (2.3)	4 (1.6)	0.77 (−1.6, 3.1) *P* = 0.5024	13 (4.8)	3 (1.2)	3.63 (0.8, 6.5) *P* = 0.0283	23 (4.5)	20 (3.8)	0.75 (−1.5, 3) *P* = 0.5327
Clinical cure rate¶, *n* (%)	6 (2.3)	6 (2.3)	−0.01 (−2.6, 2.6) *P* = 0.7078	10 (3.7)	9 (3.5)	0.17 (−3.0, 3.4) *P* = 0.5942	8 (1.6)	10 (1.9)	−0.34 (−1.8, 1.2) *P* = 0.6692
Exploratory endpoint, *n* (%)									
Subjects who achieved negative culture and ≥50% decrease in % residual involvement of the target toenail	34 (13.1)	27 (10.5)	2.66 (−2.9, 8.2) *P* = 0.2705	63 (23.3)	32 (12.5)	10.75 (4.3, 17.2) *P* = 0.0004	103 (20.3)	106 (20.3)	0.34 (−3.9, 4.5) *P* = 0.8811

*The differences are TNS-vehicle.

**The differences are TNS-amorolfine 5%.

†Complete cure rate defined as composite of negative KOH microscopy and negative culture for dermatophytes and no residual clinical involvement of the target toenail.

‡Mycological cure defined as negative microscopy and negative culture for dermatophytes.

§Clinical effectiveness defined as negative KOH microscopy and negative culture for dermatophytes and ≤10% residual involvement of the target toenail.

¶Clinical cure defined as no residual involvement of onychomycosis in the target nail.

TNS, terbinafine nail solution.

(23.3% vs. 12.5%, difference between the treatment groups [95% CI]; 10.75 [4.3, 17.2], respectively, Table 2), and in the active-controlled trial, the proportion of subjects achieving clinical cure reached 20.3% in both treatment groups (Table 2). In addition, in the sub-group of subjects achieving mycological cure, a visible clinical benefit in terms of decrease in per cent nail involvement was observed (43% for the TNS group vs. 5% reduction of % nail involvement for vehicle patients) (*data not shown*).

Exploratory analysis also showed that mycological cure could be achieved only after at least 6 months of treatment with TNS and that it took a minimum of 10 months to achieve complete cure (*data not shown*). Logistic regression analysis showed that baseline nail thickness, disease severity (as assessed by baseline nail involvement and thickness) and duration of disease are important prognostic factors for treatment success (Table 3); however, per cent nail involvement at baseline *per se* was not. Interestingly, nail thickness and per cent nail involvement were not correlated (*data not shown*). Additional analyses also showed that the younger patient population responded less favourably with mycological cure rates of 14% and 23% in patients younger and older than 55 respectively, in the TNS 48 week group. A simulation analysis based on the vehicle-controlled studies, suggested that 18 months treatment would result in a higher complete cure with an average simulated complete cure rate of 5.1% (95% CI: 2.8, 8.0) with TNS vs. vehicle 1% (95% CI: 0.0, 2.4). In 61.8% of the simulations, a statistically significant treatment difference was observed. Similarly, average simulated rates of clinical effectiveness were 14.73% (95% CI: 10.8, 19.2) for TNS and 3.6% (95% CI: 1.6, 6.0) for vehicle and in 97.6% of the simulations, clinical effectiveness rates were significantly different. Of note, the primary and secondary endpoints observed at 12 months in the simulated data were similar to those observed in the current studies.

Susceptibility testing In the vehicle-controlled studies, there was no difference in terbinafine MIC or MFC against dermatophytes post-treatment for 24 weeks or 48 weeks of treatment and there was no difference in terbinafine activity against the most commonly identified isolates, *T. rubrum* and *T. mentagrophytes*. Fungicidal activity of terbinafine against both *T. rubrum* and *T. mentagrophytes* was sufficiently high at both Week 24 [*n* (%): 218 (96) and 4 (100), respectively] and Week 48 [*n* (%): 226 (98) and 10 (83), respectively]. However, one subject in the terbinafine

Table 3 Prognostic factors for mycological cure and clinical effectiveness identified by logistic regression analysis

Prognostic factor (at baseline)		% Response rate			
		Mycology cure		Clinical effectiveness	
		TNS (%)	Vehicle (%)	TNS (%)	Vehicle (%)
Gender	Male	17	3	3	1
	Female	25	13	9	2
% Nail involved	≤40%	(NS)		9	1
	>40%			2	1
Nail thickness	≤2 mm	22	7	7	1
	>2 mm	14	4	2	2
Duration, months	≤65 months	26	6	8	2
	>65 months	12	5	1	1
Number of toenails affected	≤4	24	7	(NS)	
	>4	15	5		

Results from pooled vehicle-controlled studies.
A baseline characteristic was considered a prognostic factor (for a response) when it had a significant effect (*P*-value < 0.05) in the logistic regression model of response over treatment and the corresponding baseline characteristic.
(NS) denotes that the baseline characteristic had a *P*-value ≥ 0.05 in the logistic regression model.
TNS, terbinafine nail solution.

24-week treatment group presented a *T. rubrum* strain that had a terbinafine MIC of >64 μg/mL at baseline and at each subsequent visit. This isolate is thought to be intrinsically resistant to terbinafine.

Safety and tolerability Topical application of TNS was well tolerated (Table 4). Incidences of treatment-related adverse events (AEs) were similar across study groups and the local tolerability was comparable in the TNS and vehicle groups. None of the serious AEs were treatment-related and the incidence was comparable across study treatment groups. In the active comparator-controlled study, both TNS and amorolfine were also well-tolerated (Table 4).

Discussion

Oral terbinafine is the treatment of choice for moderate-to-severe onychomycosis and despite decades of use, fungal resistance is extremely rare. In the current studies, only one subject had an intrinsically resistant isolate to terbinafine.

Based on a favorable risk-benefit ratio for topical anti-fungal preparations with other active pharmaceutical ingredients,[14,23,34] a topical preparation of terbinafine was developed.

In the present studies, TNS was not superior to vehicle in terms of complete cure rate, although the mycological cure rate was higher in TNS, and amorolfine 5% nail lacquer did not result in any treatment benefit over and above TNS. These results are in contrast to previous studies of topical anti-fungal therapies for onychomycosis which did report higher cure rates.[23,35,36] However, many of these studies lacked vehicle control, had less strictly defined endpoints or included subjects with both finger and toe onychomycosis.[35,36]

Although the intent was to enroll subjects with mild-to-moderate onychomycosis, an analysis of the baseline profile of subjects indicates that many of them had actually quite severe disease and would have been candidates for oral treatment in routine clinical practice.[37,38] It has been suggested that higher nail involvement could result in reduced efficacy,[39] and in the present studies, the inclusion criterion was based on percentage nail involved, which, interestingly, was not a prognostic factor in the logistic regression analysis, whereas nail thickness, duration of the disease and number of nails affected were associated with a better prognosis (Table 3).

Table 4 Most frequently reported adverse events (>5% in any group) in study treatment arms by preferred term

	Vehicle-controlled double blind studies*			Active comparator-controlled study		
	Terbinafine 24 week *n* = 526 *n* (%)	Vehicle 24 week *n* = 507 *n* (%)	Terbinafine 48 week *n* = 269 *n* (%)	Vehicle 48 week *n* = 254 *n* (%)	Terbinafine 48 week *n* = 493 *n* (%)	Amorolfine 5% 48 week *n* = 512 *n* (%)
At least 1 AE	306 (58.2)	308 (60.7)	176 (65.4)	183 (72.0)	285 (57.8)	291 (56.8)
Headache	91 (17.3)	87 (17.2)	52 (19.3)	52 (20.5)	98 (19.9)	70 (13.7)
Nasopharyngitis	36 (6.8)	42 (8.3)	33 (12.3)	33 (13.0)	69 (14.0)	65 (12.7)
Influenza	10 (1.9)	8 (1.6)	19 (7.1)	14 (5.5)	25 (5.1)	15 (2.9)
Back pain	26 (4.9)	29 (5.7)	15 (5.6)	22 (8.7)	26 (5.3)	29 (5.7)
Tinea pedis	10 (1.9)	13 (2.6)	5 (1.9)	7 (2.8)	29 (5.9)	33 (6.4)
Upper respiratory tract infection	11 (2.1)	17 (3.4)	12 (4.5)	18 (7.1)	2 (0.4)	0 (0)
Sinusitis	13 (2.5)	15 (3.0)	7 (2.6)	13 (5.1)	0 (0)	12 (2.3)

*The 24 week and 48 week treatment groups were pooled for data collected up to week 28. This included a follow-up period of 4 weeks without treatment for the 24 week treatment groups.

Poor efficacy in the studies reported here may also be due to the relatively short duration of treatment, given the slow growth rate of toenails.[40,41] The conclusion that the treatment duration was too short is supported by the results of a simulation analysis which suggests that a treatment duration of 18 months is required to achieve a meaningful and demonstrable clinical benefit.

Mycological cure was achieved in a higher proportion of subjects with TNS and was associated with a greater reduction in per cent nail involvement. Mycological cure is a strong independent endpoint for evaluating topical anti-fungal agents and signifies arrest of infection.[42] On the other hand, because of the slow growth rate of toenails, there is a lag of many months following mycological cure before clinical cure, and clinical improvement may not be apparent at the time mycological cure is demonstrable. In addition, nails may appear abnormal[10] despite evidence of a complete mycological cure.[43] For example, the presence of thick nail plates may be associated with physical trauma and not with onychomycosis. Furthermore, patients with 'abnormal' nails are more likely to get infected and thus these individuals are overrepresented in the onychomycosis population. A study revealed that elderly patients were less likely to achieve clinical cure and patients with matrix involvement or slow nail growth were less likely to achieve mycological, complete and clinical cure.[44] Therefore, the stringent criteria of non-residual area of onychomycosis may not be achievable, even with adequately powered and designed studies.[42] A study of oral terbinafine or oral itraconazole with similar stringent efficacy criteria reported that only less than half of the subjects achieved disease-free toenails.[45] Mycological cure has been reported to be much higher (60–75%) than clinical cure (20–44%) in other studies as well.[46,47] Mycological cure rather than complete cure may be a more realistic and attainable endpoint for clinical trials of topical anti-fungals,[43,48] and therefore, the advisability of using 'complete cure' as the primary endpoint needs to be revisited.

Conclusions

Although the primary efficacy objective was not met, mycological cure was achieved in a higher proportion of subjects treated with TNS, and subjects with demonstrated mycological cure showed a clear clinical improvement of onychomycosis. Analyses of these results suggest that, for future trials, a change in the study design is in order. Specifically, the criteria for demonstration of effectiveness of treatment should be reexamined, along with study duration and subject inclusion criteria. These studies highlight that patient selection for topical treatment of onychomycosis is critical and that topical treatment of onychomycosis is long and challenging, with the outcome of achieving normal looking nails uncertain.

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