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ORIGINAL ARTICLE

A multicentre, randomised, parallel-group, double-blind, vehicle-controlled and open-label, active-controlled study (versus amorolfine 5%), to evaluate the efficacy and safety of terbinafine 10% nail lacquer in the treatment of onychomycosis

Ulrike Blume-Peytavi[1] | Antonella Tosti[2] | Meritxell Falqués[3] | Maria Luisa Tamarit[3] | Cristina Carreño[3] | Jordi Galván[4] | Veronica Tebbs[5]

[1]Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2]Department of Dermatology and Cutaneous Surgery, Fredric Brandt Endowed Professor of Dermatology and Cutaneous Surgery, University of Miami, Miami, Florida, USA

[3]Almirall Research and Development Center, Sant Feliu de Llobregat, Barcelona, Spain

[4]Almirall Global Medical Affairs Department, Barcelona, Spain

[5]Island View Consulting Ltd., Dronfield, UK

Correspondence
Ulrike Blume-Peytavi, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Germany.
Email: ulrike.blume-peytavi@charite.de

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Abstract

Background: Onychomycosis is a difficult-to-treat fungal nail infection whose treatment can involve systemic or topical antifungal approaches.

Objectives: To assess the efficacy and safety of terbinafine 10% nail lacquer in distal-lateral subungual onychomycosis (DLSO).

Patients/Methods: Patients with mild-to-moderate DLSO were randomised (3:3:1) to receive double-blind topical terbinafine 10% (n = 406) or its vehicle (n = 410) administered once daily for 4 weeks and then once weekly for 44 weeks, or open-label topical amorolfine 5% (n = 137) for 48 weeks, with a 12-week follow-up period. The primary efficacy endpoint, complete cure rate at Week 60, was a composite of negative potassium hydroxide (KOH) microscopy, negative culture for dermatophytes and no residual clinical involvement of the target big toenail.

Results: Complete cure rates at Week 60 in the terbinafine, vehicle and amorolfine groups were 5.67%, 2.20% and 2.92%, respectively (odds ratio (OR) vs vehicle = 2.68; 95% confidence intervals (CI): 1.22–5.86; p = .0138). Statistically significant differences in responder (negative KOH and negative culture and ≤10% residual clinical involvement) and mycological cure rates (negative KOH and negative culture) at Week 60 were obtained between terbinafine and vehicle. Terbinafine was well-tolerated with no systemic adverse reactions identified; the most common topical adverse reactions were erythema and skin irritation.

Conclusions: Terbinafine 10% nail lacquer was an effective treatment for mild-to-moderate onychomycosis improving both clinical and mycological criteria compared with vehicle. Furthermore, there may be some benefits compared to the currently available topical agent, amorolfine 5%. Treatment was well-tolerated and safe.

KEYWORDS
fungal nail infection, nail lacquer, onychomycosis, Terbinafine, topical antifungal treatment

1 | INTRODUCTION

Onychomycosis is a chronic fungal nail infection that results in thickening, discoloration, splitting of the nails and lifting of the nail plate from the nail bed, mainly affecting toes and due to dermatophytes species.[1-4]

Onychomycosis has a high incidence among the general adult population of western countries, accounting for approximately 50%–60% of all nail disorders, and can have negative consequences for patients as a result of pain or physical impairment. The poor cosmetic appearance of onychomycosis can also result in embarrassment and undermine emotional, social and occupational functioning.[5-7] It is a chronic, difficult-to-treat disease characterised by low cure rates and high relapse rates. Moreover, currently available systemic treatments suffer from limitations due to serious adverse events and possible drug-drug interactions. Topical treatments are better tolerated, but their efficacy is lower.[6]

Terbinafine hydrochloride, a synthetic allylamine, is a well-known antifungal agent that exerts its antifungal activity by non-competitive inhibition of squalene epoxidase, a key enzyme in the biosynthesis of fungal ergosterol which is essential for membrane integrity. Terbinafine has a fungistatic effect due to the depletion of ergosterol in fungal cell membranes, and a fungicidal effect resulting from the toxic accumulation of intracellular squalene.[8-10]

Terbinafine 10% nail lacquer is an antifungal formulation specifically designed for the treatment of onychomycosis due to dermatophytes and/or other terbinafine-sensitive fungi.

The aim of this randomised double-blind phase III study was to assess the efficacy and safety of terbinafine 10% nail solution in comparison with its vehicle, following 48 weeks of treatment. In addition, following an amendment to the protocol, an open-label third arm of treatment with amorolfine 5% was implemented prior to randomisation.

2 | PATIENTS AND METHODS

2.1 | Study design and treatment

This was a phase III, multicentre, randomised, parallel-group, vehicle-controlled double-blind study that aimed to evaluate the efficacy and safety of terbinafine 10% nail lacquer administered during 48 weeks. The study also included a comparison with open-label amorolfine 5%. Terbinafine 10% nail lacquer, formulated in a hydro-alcoholic solution of hydroxypropyl chitosan, was applied topically once daily for the first 4 weeks and once weekly for the remaining 44 weeks. Terbinafine 10% nail lacquer and vehicle lacquer were applied to dry nails, preferably in the evening, just before retiring to bed, to allow treated nails to remain unwashed and dry for at least 6 h. In addition, amorolfine nail lacquer 5% (Loceryl®) was used as the active comparator, being administered for 48 weeks in an open-label manner due to different posology and method of administration, with the remaining nail lacquer having to be removed and the affected nails filed before each new application.[11]

The trial was conducted between August 2015 and September 2018 and recruited a total of 953 patients from 114 sites in 13 European countries. The study was reviewed and approved by relevant Institutional Review Boards/Independent Ethics Committees and was conducted in compliance with the study protocol, the recommendations on biomedical research on human subjects included in the Declaration of Helsinki, International Conference of Harmonization-Good Clinical Practice (ICH-GCP) Guidelines, and all applicable national laws and regulations. All patients provided written informed consent.

2.2 | Patients

Male and female subjects >12 years of age with a mild-to-moderate DLSO in at least one big toenail due to dermatophytes were eligible to be screened for the study. Mild-to-moderate toe onychomycosis was clinically defined as involvement of ≥20% and ≤50% of the target big toenail area without lunula/matrix involvement, spikes/dermatophytoma or onychodystrophy, and with nail thickness not exceeding 2 mm; a positive potassium hydroxide (KOH) microscopy examination and positive culture from nail samples of the target big toenail for dermatophytes or mixed dermatophytes/*Candida* were prerequisites for randomisation. In addition, adequate reported target big toenail growth was required. Re-screening within two weeks was allowed in cases of negative KOH microscopy or culture results. Moreover, patients having positive mycology findings for the target big toenail, but with an affected area slightly less than that required by inclusion criteria could also be re-screened once within at least 1 month.

The main exclusion criteria included allergy to medications or excipients; use of cosmetic products such as nail polish on diseased nails from 24 h prior to screening until the end of the study; use of systemic antifungal drugs in the 24 weeks prior to the screening visit; nail application of topical antifungal drugs or devices in the 4 weeks prior to the screening visit; presence of nail conditions that could confuse clinical assessment (non-dermatophyte infections, onychodystrophy, dermatophytoma, presence of "yellow spikes" [defined as longitudinal streaks extending from the free edge of the nail to the proximal edge] on the target nail); nail abnormalities due to conditions such as psoriasis, lichen planus, immune dysfunction, collagen-vascular diseases and peripheral vascular disease; women who were pregnant/planning a pregnancy or breastfeeding; use of any investigational drug/device or participation in a previous clinical trial within 4 weeks of the screening visit; use of chemotherapy, immunosuppressive therapy in the 12 weeks prior to the screening visit; use of systemic corticosteroids, antimetabolites and immunostimulants in the 4 weeks prior to the screening visit; HIV infection or any other immunodeficiency; and alcohol or substance abuse.

2.3 | Study plan

The study consisted of a screening phase of up to 10 weeks, a treatment phase of 48 weeks and a 12-week follow-up period. Eight

TABLE 1 Study plan and main procedures

	Screening	Treatment						Follow-up	
		Week 0	Week 4 (± 3 days)	Week 12 (± 1 week)	Week 24 (± 1 week)	Week 36(± 1 week)	Week 48 (± 1 week)	Week 60 (± 1 week)	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Discontinuation
Dermatological assessments	X		X	X	X	X	X	X	X
Quality of life		X					X	X	X
KOH microscopy	X		X	X	X	X	X	X	X
Dermatophyte culture	X		X	X	X	X	X	X	X
In vitro susceptibility of dermatophyte isolates	X							X	X
Target nail photography	X			X	X	X	X	X	X
Skin irritation severity score			X	X	X	X	X	X	X
Evaluate acceptance of therapy							X		X

clinical examinations were planned for each patient at screening, randomisation (Week 0), treatment (Weeks 4, 12, 24, 36 and 48) and follow-up at Week 60 (Table 1). Eligible patients were randomised to treatment with terbinafine, vehicle or amorolfine according to permutated block randomisation (ratio 3:3:1).

2.4 | Efficacy and safety assessments

Patients applied the appropriate nail lacquer (terbinafine, vehicle or amorolfine) to the target big toenail and all other toenails, as well as to any fingernails suspected of fungal infection, as determined by the investigator.

A summary of procedures conducted at each visit is shown in Table 1. Demographic data, medical history/current diseases and prior and concomitant medications were recorded at screening. Dermatological assessments, KOH microscopy, culture for dermatophytes and digital photography of target nails were performed at screening, during treatment and at follow-up. In vitro susceptibility of dermatophyte isolates to terbinafine was determined at screening and follow-up visits. Clinical evaluations and digital photography of the target big toenail were conducted by the investigator, who outlined his or her assessment of the extent of the diseased area on the photograph. The images were reviewed by a single Central Blinded Evaluator (CBE), expert in onychomycosis, by reference to the clinical evaluation, with the option to revise the marking if indicated. For KOH-positive patients with acceptable images, imaging planimetry measurements were then made in order to calculate the percentage of the affected target nail area. All screening images of KOH-positive subjects and their nail planimetry data were provided to an independent panel of reviewers (IPR) consisting of four experts (3 reviewers and 1 substitute) in the field of onychomycosis, either board-certified in Dermatology or Podiatry, for the review of clinical inclusion/exclusion criteria prior to patient enrolment and subsequent randomisation.

The 17-item Onychomycosis Quality of Life questionnaire (ONYCHO© -Toenail, Mapi Research Trust)[12] assessed three categories—social problems, emotional state and the burden of symptoms during the study. Possible responses to each question were "not at all" (score 1) to "extremely bothersome" (score 5). Responses within each category were summed, and the mean calculated. Mean scores were transformed into a 0-100 scale ranging from 'extremely bothersome' (0) to 'not at all' (100).

Medication acceptability was rated by patients at Week 48 using a 4-point scale, and local tolerability at the application site was also evaluated.

2.5 | Efficacy and safety endpoints

The primary endpoint was complete cure rate at Week 60 (Visit 8:12 weeks after 48-week treatment), defined as a composite of negative KOH microscopy, negative culture for dermatophytes and

no residual clinical involvement (nail totally clear) of the target big toenail.

Secondary efficacy endpoints were responder rate at Week 60, defined as negative KOH microscopy, negative culture for dermatophytes and ≤10% residual involvement of the target toenail; mycological cure rate at Week 60, defined as negative KOH microscopy and negative culture for dermatophytes of the target toenail; and overall safety by recording all adverse events (AEs). AEs were classified by severity (mild, moderate and severe), seriousness, and causality (not related, unlikely, possible and probable) and Medical Dictionary for Regulatory Activities (MedDRA V.18.0) terminology.

Supportive efficacy endpoints were the modified cure rate at Week 60, defined as negative culture for dermatophytes and no residual clinical involvement (nail totally clear) of the target toenail; modified responder rate at Week 60, defined as negative culture for dermatophytes and ≤10% residual involvement of the target toenail; and rate of negative dermatophyte cultures for the target toenail at each visit. Patient-reported outcomes were change in ONYCHO QoL questionnaire responses from baseline to Weeks 48 and 60, and medication acceptability at Week 48.

Exploratory efficacy endpoints were evaluation of each of the three components of the primary endpoint.

2.6 | Statistical methods

2.6.1 | Sample size

Power calculations showed that inclusion of 420 patients in each treatment group would provide ≥94% power, at the 2-sided 5% level of significance, to detect a 6.7% difference in complete cure rates between terbinafine 10% nail lacquer and vehicle at 60 weeks, assuming a rate of 11% for terbinafine 10% nail lacquer and 4.3% for vehicle. In addition, approximately 140 patients were randomised to amorolfine 5% according to the established randomisation ratio of 3:3:1, and only for exploratory purposes. Overall, the total sample size was estimated to be approximately 980 patients.

2.6.2 | Study populations

The main efficacy analyses were performed on the intention-to-treat (ITT) population comprising all patients randomised and dispensed study medication. All safety analyses were conducted on the Safety population comprising all randomised patients who received at least one application of the assigned study drug. The per protocol (PP) population comprised all patients in the ITT population with a positive nail sample microscopy examination at screening involving dermatophyte(s) with or without coinfection with *Candida* spp; with confirmed clinical eligibility criteria as assessed by the IPR; who did not take forbidden medications and who completed the study without any major protocol violations. The PP population analysis was considered supportive to the ITT efficacy analysis.

2.6.3 | Statistical analysis

All statistical analyses were performed using SAS, version 9.4. All efficacy and safety variables were summarised using descriptive statistics. For the primary and the key secondary endpoints, odds ratios were calculated from the logistic regression model for complete cure adjusted by treatment group, study site and treatment-by-site interaction. In case of convergence failure of the model, the same analysis was performed excluding site factor and treatment-by-site interaction from the model. The three components of the primary endpoint (KOH, dermatophytes culture and residual clinical involvement) were summarised using descriptive statistics. Similar analyses were performed for secondary, supportive and exploratory efficacy endpoints. All efficacy analyses were performed in the ITT population using the last observation carried forward (LOCF) approach for missing values. Primary efficacy and exploratory efficacy analyses (ie the single components of the complete cure rate) were repeated in the PP population to assess the robustness of the results. Furthermore, five sensitivity analyses for handling missing data were performed: complete-, best- and worst-case analysis, discrete repeated measure analyses, and a multiple imputation analysis using a Monte Carlo Markov Chain (MCMC) simulation. The overall type I family-wise error rate for testing the primary and the two key secondary efficacy endpoints was controlled at the 5% significance level using a two-step serial gatekeeping multiple comparison procedure, and the Holm-Bonferroni method in the second step where the key secondary endpoints were tested.

ONYCHO results were calculated using an analysis of covariance (ANCOVA) model for the change in scores from baseline to Week 60 using the baseline value as a covariate; and treatment group, site and treatment-by-site interaction as factors.

For all inferential analyses, two-sided p-values ≤ .05 were considered statistically significant.

3 | RESULTS

3.1 | Patient disposition and demographics

Over a 10-week period, a total of 4944 persons were screened for mild-to-moderate DLSO due to dermatophytes involving ≥20% to ≤50% of a target big toenail, and 953 patients were randomised to receive terbinafine (n = 406), vehicle (n = 410) or amorolfine (n = 137) as the ITT population. Overall, 822 patients completed the study, and the PP population consisted of 799 patients. Patient disposition is summarised in Figure 1.

Demographic and baseline characteristics of the ITT population are summarised in Table 2. The population had a mean age around 59 years, were almost exclusively Caucasian (>99%) and included slightly more males than females. The mean area of the target big toenail affected was about 35%, and the number of affected toenails

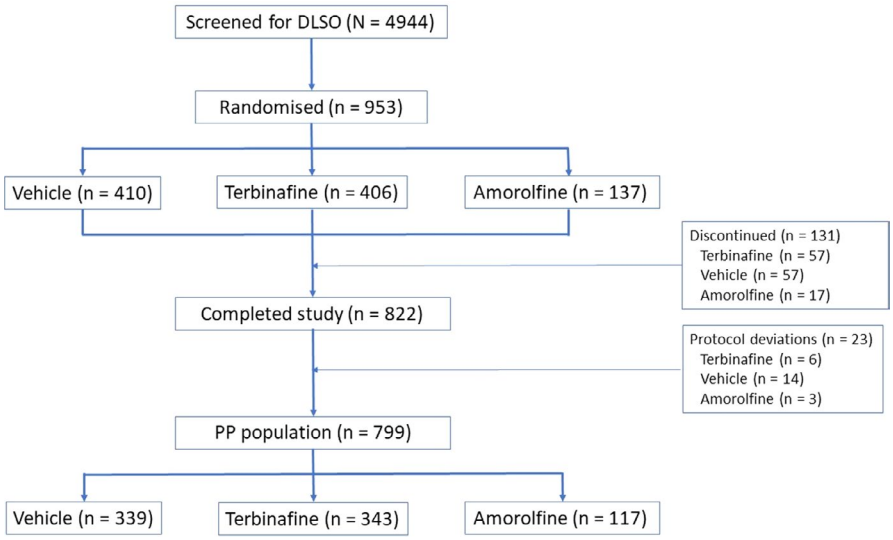

FIGURE 1 Patient disposition. DLSO, distal-lateral subungual onychomycosis; PP, per protocol

was almost 5 in all groups. Positive screening cultures showed the presence of *Trichophyton rubrum* in around 80% of cases. Most patients (>90%) had no clinical evidence of infection of the fingernails.

3.2 | Efficacy

3.2.1 | Primary efficacy outcome

Complete cure rates at Week 60 (ITT population, LOCF approach) were higher in the terbinafine group (5.67%) compared with the vehicle (2.20%) and amorolfine (2.92%) groups. Patients treated with terbinafine had a statistically significant higher complete cure rate compared with vehicle ($p = .0138$), but not amorolfine ($p = .2095$) (Table 3). Odds ratios for comparisons of terbinafine with vehicle and with amorolfine are shown in Table 3 and graphically in Figure 2.

The most common reason for failure to achieve the composite primary endpoint (at Week 60) in terbinafine and amorolfine treatment groups was a negative dermatophyte culture but with KOH microscopy positivity and residual clinical involvement of the target nail. This response pattern was observed in 61.58% ($n = 250$), 47.45% ($n = 65$) and 34.63% ($n = 142$) of patients in the terbinafine, amorolfine and vehicle groups, respectively. In contrast, the most common pattern seen in the vehicle group (45.61%; $n = 187$) was failure for all three components, that is positivity for KOH microscopy and dermatophyte culture, and some residual clinical involvement of the target nail.

TABLE 2 Demographic and baseline characteristics (ITT population)

Parameter	Terbinafine 10% ($n = 406$)	Vehicle ($n = 410$)	Amorolfine 5% ($n = 137$)
Age (years): mean (SD)	58.99 (12.65)	59.19 (13.06)	58.19 (12.72)
Gender, *n* (%) Male	226 (55.67)	253 (61.71)	85 (62.04)
Female	180 (44.33)	157 (38.29)	52 (37.96)
Race, *n* (%): White	405 (99.75)	407 (99.27)	137 (100.00)
Black/African American	0	1 (0.24)	0
Asian	0	1 (0.24)	0
American Indian/Alaskan Native	0	1 (0.24)	0
Other	1 (0.25)	0	0
Area of target big toenail affected (%), mean (SD)	34.72 (9.92)	34.82 (10.14)	35.23 (10.11)
Number of affected toenails, mean (SD)	4.81 (2.90)	4.65 (2.81)	4.96 (2.73)
Screening culture for the target big toenail, *n* (%)			
Trichophyton rubrum	319 (78.57)	347 (84.63)	107 (78.10)
Trichophyton mentagrophytes	61 (15.02)	44 (10.73)	14 (10.22)
Other species	36 (8.9)	24 (5.9)	17 (12.4)

Note: NB Each patient could be positive for more than one dermatophyte species.

TABLE 3 Primary, and main secondary and supportive efficacy endpoints in the ITT population (LOCF approach)

	Terbinafine ($n = 406$)	Vehicle ($n = 410$)	Amorolfine ($n = 137$)	Terbinafine *vs* Vehicle	Terbinafine *vs* Amorolfine
	n (%)			Odds Ratio (95% CI); *p* value	
Primary efficacy endpoint					
Complete cure rate at Week 60	23 (5.67)	9 (2.20)	4 (2.92)	2.68 (1.22–5.86); 0.0138	2.00 (0.67–5.88); 0.2095
Secondary efficacy endpoints					
Responder rate at Week 60	27 (6.65)	14 (3.41)	5 (3.65)	2.02 (1.04–3.90); 0.0377	1.88 (0.71–4.98); 0.2040
Mycological cure rate at Week 60	83 (20.44)	50 (12.20)	26 (18.98)	1.85 (1.26–2.71); 0.0016	1.10 (0.67–1.79); 0.7113
Supportive efficacy endpoints					
Modified cure rate at Week 60	42 (10.34)	28 (6.83)	5 (3.65)	1.57 (0.96–2.59); 0.0749	3.05 (1.18–7.86); 0.0213
Modified responder rate at Week 60	57 (14.04)	40 (9.76)	7 (5.11)	1.51 (0.98–2.32); 0.0600	3.03 (1.35–6.82); 0.0073

Abbreviations: 95% CI, 95% confidence interval; ITT, intention-to-treat; LOCF, last observation carried forward.

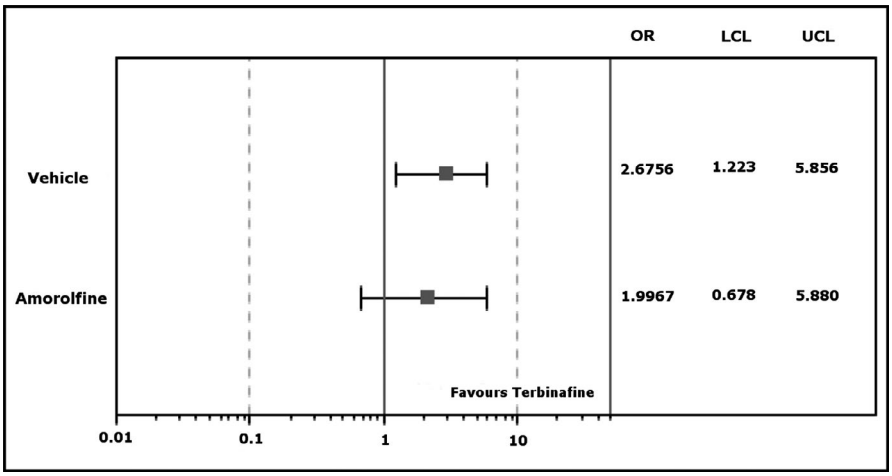

FIGURE 2 Results of logistic regression analysis of complete cure rate at Week 60 (LOCF approach; ITT population) comparing terbinafine with vehicle or amorolfine. LCL, lower confidence limit; OR, odds ratio; UCL, upper confidence limit

Comparable results for the primary endpoint were obtained in the PP population and after using different imputation schemes for missing data in the ITT population.

3.2.2 | Secondary efficacy outcomes

Responder rates at Week 60 were higher in the terbinafine group (6.65%) compared with vehicle (3.41%) and amorolfine (3.65%) groups. Week 60 mycological cure rates were 20.44%, 12.20% and 18.98%, respectively. Patients in the terbinafine group had significantly higher responder rates ($p = .0377$) and mycological cure rates ($p = .0016$) compared with vehicle (Table 3).

3.2.3 | Supportive and exploratory endpoints

Supportive efficacy outcomes

Modified cure rates at Week 60 were superior in the terbinafine group (10.34%) compared with vehicle (6.83%) and amorolfine (3.65%) groups. Similarly, modified responder rates at Week 60 were higher with terbinafine (14.04%) than with vehicle (9.76%) or amorolfine (5.11%). Statistically significant differences between terbinafine and amorolfine groups were demonstrated for modified cure rates ($p = .0213$) and modified responder rates ($p = .0073$) (Table 3).

Exploratory efficacy endpoints

Analysis of the individual components of the composite primary efficacy endpoint (ITT population, LOCF approach) showed that patients treated with terbinafine experienced a statistically significantly improvement in negative KOH microscopy results (OR, 1.68; 95% CI:1.16–2.44; $p = .0060$) and negative dermatophyte culture (OR, 6.15; 95% CI: 4.35–8.69; $p < .0001$) at Week 60 compared with the vehicle group. However, there was no significant difference between terbinafine and vehicle regarding no residual clinical involvement of the target toenail (OR, 1.24, 95% CI: 0.77–1.98; $p = .3777$). Comparison of terbinafine with amorolfine for negative KOH microscopy results at Week 60 showed no significant difference (OR, 1.11; 95% CI: 0.68–1.82; $p = .6666$). However, when compared with amorolfine, patients treated with terbinafine demonstrated statistically significant better results at Week 60 for both negative dermatophyte culture (OR, 3.19; 95% CI: 2.02–5.04; $p < .0001$) and no residual clinical involvement of the target toenail (OR, 2.52; 95% CI: 1.05–6.06; $p = .0393$).

Patient-reported outcomes

Comparable results between treatment groups were found at Week 60 for the ONYCHO© questionnaire components social problems and emotional state. Patients in the terbinafine group reported significant improvement in the burden of symptoms compared to amorolfine (6.79 vs 12.68; $p = .0200$). Burden of symptoms in the terbinafine and vehicle groups was comparable (Table 4).

The majority of patients rated the acceptance of therapy as good/very good, with a similar proportion in all treatment groups: 55.62%, 54.76% and 58.34% in the terbinafine, vehicle and amorolfine groups, respectively. However, a higher proportion in the vehicle group rated acceptance as poor: 20.05%, compared to 15.14% in the terbinafine group and 16.67% in the amorolfine group.

3.3 | Safety

In the safety analysis set, mean treatment compliance was high: 98.8%, 99.0% and 99.3% in the terbinafine ($n = 406$), vehicle ($n = 407$) and amorolfine ($n = 137$) groups, respectively. The most frequent TEAEs reported by System Organ Class (SOC) were 'Infections and Infestations' ($n = 155$, 16.32%), especially nasopharyngitis ($n = 90$, 9.47%). Other frequently reported TEAEs were headache ($n = 42$, 4.42%), back pain ($n = 28$, 2.95%), hypertension ($n = 26$, 2.74%) and bronchitis ($n = 23$, 2.42%), with no relevant differences between the three groups. The outcome for most TEAEs was 'recovered/resolved'.

Overall, 423 of 950 patients (44.53%) in the safety population had one or more TEAEs, with a slightly lower incidence in the terbinafine group (41.87%; $n = 170$) compared with the vehicle (46.68%; $n = 190$) and amorolfine (45.99%; $n = 63$) groups. A total of 1086 TEAEs were reported comprising 456, 476 and 154 events in the terbinafine, vehicle and amorolfine groups, respectively (Table 5).

A total of 52 patients (5.47%) had serious TEAEs with a similar incidence in the terbinafine (5.17%) and vehicle (5.41%) groups, and a slightly higher incidence in the amorolfine group (6.57%). Most reported TEAEs were mild in severity, but 39 patients (4.11%) reported one or more severe TEAEs: rates in the terbinafine, vehicle and amorolfine groups were 4.19%, 3.44% and 5.84%, respectively. Drug-related TEAEs, defined strictly as any AEs with a causal relationship to study drug of probable, possible or unlikely in the opinion of the investigator, were reported in 35 patients (3.68%): with similar rates in terbinafine (3.94%), vehicle (3.44%) and amorolfine (3.65%) groups (Table 5). The most commonly reported TEAEs suspected to be related to the study drug were categorised as 'skin and subcutaneous tissue disorders' ($n = 18$, 1.89%). However, most patients (>94%) in each treatment group had no evidence of irritation of the toenails or the surrounding skin at each study visit. Only one patient (in the vehicle group) had some evidence of fingernail irritation (at Week 24).

The incidence rates of new toenail irritation events were very low (<1%) and similar in all treatment groups.

Five patients (0.53%) discontinued treatment due to a TEAE: 4 (0.99%) in the terbinafine group and 1 (0.25%) in the vehicle group. Two patients (0.21%) discontinued due to a TEAE assessed as 'unlikely' by the investigator, but analysed as drug related: 1 (0.25%) in the terbinafine group (epilepsy, severe) and 1 (0.25%) in the vehicle group (onychomadesis, moderate). One patient in the terbinafine group discontinued treatment due to a non-drug related TEAE (mild arthralgia), and two patients (0.49%) in this group had a fatal TEAE (pancreatic carcinoma and cerebrovascular accident, which were considered not to be related to treatment by the investigator).

No differences between treatment groups in mean haematology, serum chemistry and urinalysis parameters were detected throughout the study.

4 | DISCUSSION

Onychomycosis is a chronic fungal infection of the nails that results in thickening, discoloration, splitting of the nails and lifting of the nail plate from the nail bed. Toenails are more often affected than fingernails by a ratio of about 4:1.[1-3] Dermatophytes, including the genera *Microsporum*, *Epidermophyton* and *Trichophyton*, are the main causal organisms responsible for toenail infections, and cause 50% of fingernail infections. Commonly, *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the pathogenic species involved. Non-dermatophyte moulds (including *Scopulariopsis, Aspergillus and Fusarium*), yeasts (including *Candida albicans and Candida parapsilosis*) or a combination of fungi may also be involved, although are much less common.[4]

Currently available systemic treatments for onychomycosis have low cure rates and high relapse rates and may be limited due to serious adverse events and possible drug-drug interactions. Topical treatments are better tolerated, but their efficacy is lower. Approved oral onychomycosis therapies include terbinafine and

TABLE 4 Analysis of changes from baseline to Week 60 in the ONYCHO questionnaire domains (ITT population; LOCF approach)

	Terbinafine ($n = 406$)	Vehicle ($n = 410$)	Amorolfine ($n = 137$)	Terbinafine vs Vehicle	Terbinafine vs Amorolfine
	LSM (*SE*)			*p* Value	
Social problems	4.97 (1.31)	5.15 (1.30)	5.23 (2.31)	0.9947	0.9948
Emotional state	6.27 (0.99)	6.04 (0.99)	8.96 (1.75)	0.9862	0.3736
Burden of symptoms	6.79 (1.08)	6.34 (1.08)	12.68 (1.91)	0.9528	0.0200

Abbreviations: LSM, least square mean; *SE*, standard error.

TABLE 5 Treatment-emergent adverse events (TEAEs) in the safety population

Parameter	Terbinafine 10% ($n = 406$)	Vehicle ($n = 407$)	Amorolfine 5% ($n = 137$)	Total ($n = 950$)
Patients with any TEAE, *n* (%)	170 (41.87)	190 (46.68)	63 (45.99)	423 (44.53)
Any TEAE, *n*	456	476	154	1086
Patients with serious TEAEs, *n* (%)	21 (5.17)	22 (5.41)	9 (6.57)	52 (5.47)
Patients with severe TEAEs, *n* (%)	17 (4.19)	14 (3.44)	8 (5.84)	39 (4.11)
Patients with drug related TEAEs, *n* (%)	16 (3.94)	14 (3.44)	5 (3.65)	35 (3.68)
Patients with drug related serious TEAEs, *n* (%)	0	0	0	0
Patients with drug related severe TEAEs, *n* (%)	1 (0.25)	0	0	1 (0.11)
Patients with TEAEs leading to discontinuation, *n* (%)	4 (0.99)	1 (0.25)	0	5 (0.53)
Patients with drug related TEAEs leading to discontinuation, *n* (%)	1 (0.25)	1 (0.25)	0	2 (0.21)
Patients with fatal adverse events, *n* (%)	2 (0.49)	0	0	2 (0.21)

itraconazole, and in Europe, fluconazole is recommended when other agents are not considered appropriate.[6,13] Preference for oral terbinafine is based on its better cure rates and fewer drug-drug interactions. Topical approved therapies in Europe include ciclopirox 8% (in water-soluble or insoluble formulations), amorolfine 5% and tioconazole nail lacquers. However, there is still no treatment that achieves high mycological and complete cure rates and recurrence following onychomycosis therapy is common.[14]

Terbinafine is a non-competitive inhibitor of squalene epoxidase.[9] The consequences of squalene epoxidase inhibition are twofold: a fungistatic effect as a result of ergosterol depletion from fungal cell membranes that contributes to impaired growth of the pathogen, and also a fungicidal effect due to the intracellular accumulation of squalene, which perturbs phospholipid membranes and results in cell death.[2,10] However, oral terbinafine is associated with AEs including hepatotoxicity that may occur in patients with or without pre-existing liver disease. Consequently, monitoring of liver function before initiating terbinafine therapy is recommended and, where indicated by a patient's medical history and/or concomitant medications, potentially also during therapy.[14] Topical formulations of terbinafine in the form of 1% solutions, creams, gels and sprays, with low systemic exposure, are approved for the treatment of fungal skin infections, but are not specifically indicated for the treatment of onychomycosis.

Pharmacokinetic (PK) studies of the present formulation of terbinafine 10% (hydro-alcoholic solution of hydroxypropyl chitosan [HPCH]) showed that when administered in the current initial dosing schedule (once daily for 4 weeks, before reducing to once weekly) terbinafine concentrations in the target tissue, the nail, were more than 3 orders of magnitude higher than those obtained after oral terbinafine administration (1.01 μg/kg),[15] achieving steady-state concentrations of about 10,000 μg/g after the initial 4-week priming period and as high as 1000 μg/g 24 weeks after the end of the treatment. Measured terbinafine nail concentrations were significantly higher than published in vitro minimum inhibitory concentrations (MIC) against relevant pathogenic fungi.[16] By contrast, mean terbinafine plasma concentrations were 1000 times lower than those obtained after oral terbinafine administration (C_{max} = 1.70 μg/ml after a dose of 250 mg),[17] thus offering the potential for a clinical response while avoiding possible adverse reactions related to systemic exposure.

Terbinafine 10% nail lacquer had a superior and statistically significant complete cure rate at Week 60 (primary efficacy outcome) compared with vehicle. The secondary efficacy outcomes, responder and mycological cure rates at Week 60 were also significantly higher with terbinafine. Although each of these outcomes was higher with terbinafine compared with amorolfine, the differences were not statistically significant. This reflects the exploratory comparison of terbinafine with amorolfine, with patients randomised 3:1, in favour of terbinafine. Further larger studies are needed to demonstrate the relative efficacy of these two topical agents.

Previous clinical trials of an alternative formulation of a topical terbinafine as a nail solution for mild-to-moderate toenail onychomycosis failed to show any significant difference in the complete cure rate when compared to vehicle alone or the active comparator, amorolfine.[18] Formulation of topical agents is complex, and it may be that differences in clinical outcomes are influenced by the inclusion of HPCH in the topical 10% nail lacquer formulation, as used in this study.

Most clinical trials evaluating oral and topical drugs for treating onychomycosis have been of 48–52 weeks duration to measure efficacy, and commonly used mycological and clinical assessments to assess therapeutic outcomes. However, mycological assessment may include both culture and KOH microscopy. In situations where 'cure' in terms of all 3 endpoints is required to define treatment success introduces significant complexity, with the added problem of inconsistency in the definitions of clinical cure and almost complete cure which needs to be addressed.[19,20] One suggested definition of onychomycosis cure is the absence of clinical signs following an adequate washout period, together with a negative dermatophyte culture, and with or without negative microscopy, to avoid the confounding factor of identifying hyphae on microscopy which are non-viable.[20]

Onychomycosis can cause physical and psychological distress to patients. Studies show that patients who achieved clinical improvement reported statistically significant differences in treatment satisfaction scores for QoL outcome measures compared with patients who reported no clinical improvement following treatment.[5] In the present study, terbinafine significantly reduced the burden of symptoms compared with amorolfine, although results in the ONYCHO questionnaire for all three domains between terbinafine and vehicle were similar.

The safety profile of topical terbinafine showed that the agent was well-tolerated with no important adverse reactions arising, consistent with the findings of the previous study on the different formulation.[18] Compliance was generally high and acceptance good in all treatment groups. In contrast, adverse drug reactions (ADRs) have been reported for orally administered terbinafine. Most ADRs of oral terbinafine involve the gastrointestinal system and skin, and are generally mild-to-moderate in severity and transient. While gastrointestinal symptoms are very common, rarely serious hepatic dysfunction may occur, although most cases involve asymptomatic and reversible elevation of liver enzymes.[21-23]

In conclusion, the results of the present study indicate that topical terbinafine is an effective treatment with respect to both clinical and mycological criteria when compared with vehicle for patients with mild-to-moderate onychomycosis of the distal-lateral subungual type. In addition, results suggest that there may be some benefits compared to the currently available topical agent, amorolfine. Overall, this newer formulation of topical terbinafine was safe to use and well-tolerated, producing very few adverse local effects.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTION

Ulrike Blume-Peytavi: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Antonella Tosti:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Meritxell Falqués:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Maria Luisa Tamarit:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Cristina Carreño:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Jordi Galván:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Veronica Tebbs:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Clinical Trials Register at https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000561-31/results.

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