A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement

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Conflicts of interest
The investigating authors received honoraria for conducting the studies, and work as consultants for Galderma Laboratories; Farzaneh Sidou and Nabil Kerrouche are employees of Galderma R&D. The authors have no other financial interests to disclose.

Summary

Background Onychomycosis is common, accounting for up to 50% of all nail disorders. Toenail onychomycosis can cause nail deformity, embarrassment, pain and walking difficulties. Some populations, such as individuals with diabetes, are at higher risk for developing secondary complications such as infections. Treatment takes many months and therapeutic choices can increase clinical effectiveness, lower toxicity and minimize healthcare costs.

Objectives Based on the results of a previous pilot study, the objective of the present study was to show, in a larger population, the enhanced efficacy of a combination of amorolfine nail lacquer and oral terbinafine in the treatment of onychomycosis with matrix involvement. In addition, a cost-effectiveness analysis was performed.

Methods In this multicentre, randomized, open-label, parallel group study, patients were randomized to receive either a combination of amorolfine hydrochloride 5% nail lacquer once weekly for 12 months plus terbinafine 250 mg once daily for 3 months (AT group) or terbinafine alone once daily for 3 months (T group). The study duration was 18 months including a 6-month treatment-free phase following the 12-month active treatment phase for the AT group and a 15-month treatment-free phase following the 3-month active treatment phase for the T group. The primary efficacy criterion was overall response, dichotomized into success or failure, success being the combination of clinical cure and negative mycology at month 18. This criterion was used as the effectiveness measure in the pharmacoeconomic analysis, conducted from a payer perspective.

Results In total, 249 patients were included into the study: 120 in the AT group and 129 in the T group. A significantly higher success rate was observed for patients in the AT group relative to those in the T group at 18 months (59.2% vs. 45.0%; P = 0.03). Both treatment regimens were safe and well tolerated. Treatment cost per cured patient was lower for the combination than for terbinafine alone in all countries.
Conclusions Study results confirmed that, in the treatment of dermatophytic toenail onychomycosis with matrix involvement, amorolfine nail lacquer in combination with oral terbinafine enhances clinical efficacy and is more cost-effective than terbinafine alone.

Onychomycosis is a common fungal infection of the nail unit, accounting for up to 50% of all nail disorders.1–4 Approximately 2–10% of the adult population are affected by the condition and the prevalence rises with age, with approximately 14–28% of those above 60 years of age affected.5–7 Onychomycosis is mainly caused by dermatophyte infections, with greater than 80% involving Trichophyton rubrum.8 Without proper treatment, onychomycosis can cause psychosocial and physical problems, significantly impacting quality of life.9,10 Various topical and oral treatment options are available for the management of onychomycosis.5,11 Treatment guidelines suggest that topical treatments are appropriate for early and mild forms of the disease, such as when the distal part of the nail is affected. In patients who did not respond to a 6-month topical treatment or in more severe cases, such as those involving the nail matrix, or with lateral edge involvement, systemic treatment is indicated.

However, with relapses and re-infections being common and standard systemic treatments resulting in less than 50% of patients achieving disease-free nails,12 onychomycosis remains difficult to treat. In the past, combination therapy has been demonstrated to be an effective and safe alternative treatment approach in patients who do not respond to monotherapy or as first-line therapy for patients who may benefit from a more aggressive therapy.1

Management of onychomycosis is costly. The direct cost of treating onychomycosis was estimated as $43 million per year by U.S. Medicare.13 Hence, the therapeutic approach should be based on a long-term strategy, taking into account the basic concepts of pharmacoeconomics: weighing costs of treatment (input) against efficacy (outcome).

Amorolfine, a morpholine derivative with potent antifungal properties,14 is available in a 5% nail lacquer in many countries worldwide. Harman et al. demonstrated a synergistic activity in vitro for some combinations of topical amorolfine and oral antifungal therapies, suggesting that this synergy may improve clinical cure rates.15 Further research in humans demonstrated that enhanced efficacy exists when treatment with once-weekly amorolfine nail lacquer is combined with standard systemic therapies for onychomycosis.5,14–17

In a previous pilot study, the combination of topical amorolfine and oral terbinafine, the most widely prescribed oral antifungal agent, resulted in markedly improved mycological and clinical outcomes as well as a better cost per cure ratio for combination therapy.16 The objective of the present study was to confirm these results and to determine if an enhanced efficacy exists when amorolfine nail lacquer is used in combination with oral terbinafine in a larger cohort of patients with dermatophytic toenail onychomycosis and matrix involvement. The study also included two exploratory variables, the presence of streaks and/or onycholysis on the target toenail at baseline, which were analysed for a possible predictive relationship with the overall response rate of combination therapy. Finally, the cost-effectiveness of the combination of amorolfine nail lacquer with terbinafine was compared with that of terbinafine alone.

Materials and methods

The study was conducted in accordance with the principles of current international ethical standards originating from the Declaration of Helsinki and in compliance with local regulatory requirements and was reviewed and approved by Independent Ethics Committees. All patients provided their written informed consent prior to entering the study.

Study design

The efficacy and safety of the combination of amorolfine nail lacquer plus terbinafine were compared with those of terbinafine alone in an 18-month, multicentre, randomized, open-label, and parallel group study in patients with dermatophytic onychomycosis and matrix involvement. The study was conducted at 20 centres in nine European countries between February 2002 and September 2004. A 1:1 ratio randomization list was specifically generated for this study. Suitable patients received in chronological order, corresponding to their inclusion into the study at baseline, either a combination therapy of amorolfine hydrochloride (Loceryl® 5% nail lacquer; Galderma, Lausanne, Switzerland) once weekly for 12 months and terbinafine (Lamisil® 250 mg tablets; Novartis, Basel, Switzerland) once daily for 3 months (AT group) or terbinafine alone once daily for 3 months (T group). The study duration was 18 months; a 6-month treatment-free phase followed the 12-month active treatment phase for the AT group and a 15-month treatment-free phase followed the 3-month active treatment phase for the T group. Patients were evaluated at baseline and at months 1, 3, 6, 9, 12, 15 and 18. A pregnancy test was required at screening and after completion of terbinafine therapy (3-month visit) for all women of child-bearing potential.

At screening visit, investigators selected a pathological target nail to be sampled for mycological follow-up. All samples were sent to a single reference laboratory (Professor E.G.V. Evans, Cardiff, U.K.) for direct microscopic examination and mycological culture. For direct microscopy, nail specimens were placed in 20% potassium hydroxide solution. Cultures were maintained at room temperature for up to 4 weeks using
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Saboraud dextrose agar with 0.005% chloramphenicol and 0.05% actidione.16

Patients

Men and women aged 18–70 years with dermatophytic onychomycosis affecting at least one great toenail (target nail) and matrix involvement were screened for enrolment. Eligible patients were required to have dermatophytes from both direct microscopic and mycological culture examinations. Patients should have had a washout period of at least 3 months for antifungal nail lacquers and of 6 months for oral antifungals. Exclusion criteria prohibited enrolment of patients with predisposing conditions such as diabetes or other peripheral circulatory disorders, psoriasis, lichen planus or human immunodeficiency virus; patients with known sensitivities to study treatments, patients requiring interfering treatment; and patients with impaired liver and/or kidney function. Women were excluded if they were pregnant, breast-feeding, or planning a pregnancy.

Efficacy and safety assessments

The primary efficacy variable was the overall response at endpoint (month 18, intent-to-treat (ITT) population, last observation carried forward (LOCF)) using a dichotomous scale of success or failure. Success was defined as the combination of clinical cure (i.e. disappearance of all lesions on each nail or residual disease of no more than 10% of the original total diseased surface) and negative mycology comprising both negative direct microscopy and negative culture (Table 1). Secondary efficacy assessments included: clinical response (failure, improvement or cure), mycological examination of the target nail (direct microscopy and mycological culture), and total percentage diseased surface. A 19-question onychomycosis quality-of-life questionnaire was completed at baseline and at endpoint by a subset of study patients in France, Germany and Italy, where the questionnaire was culturally validated.7 In addition, two exploratory criteria were assessed during the study: the presence of streaks and of onycholysis on the target nail was assessed at baseline, followed by a subgroup analysis of the primary efficacy criterion according to the presence or absence of these characteristics. A yellow streak is a variant of dermatophyma. It presents as a distal to proximal yellow-white spike. It may be single or multiple.

Safety was assessed through adverse events and laboratory monitoring. Throughout the course of the study, adverse events were recorded by the investigators with a clinical determination of severity and relationship to study drug. Liver and kidney function were checked at screening and after completion of terbinafine therapy (month 3 visit).

Cost-effectiveness evaluation

The primary efficacy criterion, overall response at the last visit, was chosen as efficacy measure. The pharmacoeconomic evaluation was conducted from the payer’s perspective in every country. Only direct costs related to the drug acquisition were included. Other costs were not considered as both groups followed the same evaluations (diagnostic tests, physician visits, laboratory tests etc.) and because only few adverse events occurred. The mean quantity of amorolfin nail lacquer used per patient was based on a specific study evaluating the quantity of nail lacquer required to treat an onychomycosis-infected nail.18 For terbinafine, the quantity used was based on the protocol indication. Local public prices of amorolfin 5% nail lacquer and terbinafine 250 mg were considered. When several pack sizes were available, drug costs were calculated to be minimized.

Statistical analyses

A sample size of 125 patients per group was deemed necessary to detect a 20% clinically relevant difference between the

<table>
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<th>Table 1 Definitions for efficacy assessments</th>
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<td><strong>Primary efficacy criterion</strong></td>
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<td>Overall response: dichotomous scale, at month 18 (ITT, LOCF)</td>
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<td>Failure</td>
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<tr>
<td>Success</td>
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<td>Secondary efficacy criteria</td>
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<tr>
<td>Clinical response: full scale (ITT, LOCF)</td>
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<tr>
<td>Failure</td>
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<td>At least 20% reduction in the total diseased surface from baseline</td>
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<td>Disappearance of all lesions on each nail or residual disease of no more than 10% of the original total diseased surface (the remaining diseased surface on all affected nails should involve only the distal third)</td>
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<tr>
<td>Mycological examination: dichotomous scale (ITT, LOCF)</td>
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<tr>
<td>Negative</td>
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<tr>
<td>Both negative direct microscopy and culture results</td>
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<td>Positive direct microscopy and/or positive culture results</td>
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two treatment groups based on the results of a previous study\textsuperscript{16} and assuming a dropout rate of 20%.

The primary statistical analysis was performed on the ITT population, i.e. in all patients enrolled and randomized. The LOCF methodology was used to account for missing data for the ITT population analysis. The safety population was defined as all patients randomized and treated at least once.

The analysis of all efficacy criteria was performed using the Cochran–Mantel–Haenszel test stratified by ‘pseudocentre’ (cluster of study centres set up by regional area) and ridit transformation. All tests were two-sided and used the 0.05 level to declare significance. No adjustment for multiplicity was made.

Adverse events were based on the safety population. Results were summarized by their relationship to the study drugs and by their severity (i.e. mild, moderate or severe).

## Results

### Patient disposition and baseline characteristics

In total, 249 patients were randomized and included into the ITT population: 120 received amorolfine plus terbinafine (AT group) and 129 received terbinafine alone (T group). Overall, 83.5% of all patients completed the study. Discontinuation rates were higher in the T group (20.2%) than in the AT group (12.5%), mainly due to differences in the percent-age of patients who discontinued due to lack of efficacy (5.4% in the T group vs. 0.8% in the AT group) and to patient request (5.4% in the T group vs. 1.7% in the AT group). Baseline characteristics of the ITT population are summarized in Table 2. These characteristics were comparable between the two treatment groups. Figure 1 presents the patient flow throughout the study.

Major protocol deviations were reported for 67 patients (27%), with a higher incidence in the T group (44 patients; 34%) compared with the AT group (23 patients; 19%). The most common protocol deviation in both treatment groups was associated with the 18-month visit either not being completed (16%) or being outside of the protocol-specified timeframe (8%).

### Efficacy evaluation

Success rates at each study visit are presented in Figure 2. At endpoint (month 18; ITT, LOCF), treatment with the amorolfine-terbinafine combination resulted in a significantly higher success rate (59.2%) compared with treatment with terbinafine alone (45.0%; \(P = 0.03\)). During the course of the study, the success rate in the AT group increased at each evaluation following baseline, with an evident numerical difference between the treatment groups beginning at month 12. In terms of clinical response, patients in the AT group were significantly more likely to be clinically cured at month 18 than

| Table 2 Baseline demographics and disease characteristics (intent-to-treat population) |
|---------------------------------|------------|----------|-----------|
|                                | AT group   | T group  | Total     |
|                                | (n = 120)  | (n = 129)| (n = 249) |
| Sex, n (%)                     |            |          |           |
| Male                           | 82 (68.3)  | 87 (67.4)| 169 (67.9)|
| Female                        | 38 (31.7)  | 42 (32.6)| 80 (32.1) |
| Age, years                     |            |          |           |
| Mean ± SD                     | 46.8 ± 13.3| 47.8 ± 12.6| 47.3 ± 12.9|
| Median                        | 46.8       | 49.7     | 48.6      |
| Range                         | 20–8–70.8  | 20–4–72.5| 20–4–72.5|
| Race, n (%)                   |            |          |           |
| White                         | 115 (95.8)| 126 (97.7)| 241 (96.8) |
| Black                         | 2 (1.7)   | 2 (1.6)  | 4 (1.6)   |
| Asian                         | 2 (1.7)   | 1 (0.8)  | 3 (1.2)   |
| Other                         | 1 (0.8)   | –        | 1 (0.4)   |
| % total diseased surface \(a\) | 120 (100.0)| 129 (100.0)| 249 (100.0)|
| Mean ± SD                     | 253 ± 197  | 234 ± 171| 244 ± 184 |
| Range                         | 30–880     | 25–720   | 25–880    |
| Causative organisms, n (%)    |            |          |           |
| Acremonium species            | 0          | 1 (0.8)  | 1 (0.4)   |
| Socoreusis bresulix           | 0          | 2 (1.6)  | 2 (0.8)   |
| Trichophyton interdigitale    | 1 (0.8)   | 0        | 1 (0.4)   |
| Trichophyton mentagrophytes   | 5 (4.2)   | 6 (4.7)  | 11 (4.4)  |
| Trichophyton rubrum           | 112 (93.3)| 120 (93.0)| 232 (93.2) |
| Missing                       | 2 (1.7)   | 0        | 2 (0.8)   |

The AT group received amorolfine plus terbinafine, while the T group received terbinafine only. \(a\)Combination of direct microscopy and culture results. \(b\)Total diseased surface was determined by summation of the diseased surfaces of all affected nails.
those treated with terbinafine (66.7% vs. 53.5%, respectively; P < 0.04; Fig. 3).

Both treatment groups showed important reductions in the percentage of the total diseased surface on the target nail, with mean reductions of 85.1% for the AT group and 78.5% for the T group at month 18. Similarly, the mycological examination showed a higher number of mycologically cured patients (defined as negative results on both direct microscopy and culture) in the AT group than in the T group from month 6 onwards (Fig. 4a). The overall mycological examination results mirrored the direct microscopy results (Fig. 4b), as mycotic structures visible microscopically may still be present long after all of the dermatophytes have been eliminated.

Results from the mycological culture showed larger differences between the treatment groups compared with direct microscopy. Significant differences in the percentage of patients

![Patient flow chart](image1.png)

![Graphs showing success rates](image2.png)

![Graphs showing clinical response](image3.png)

![Graphs showing incidence of negative mycological examination](image4.png)

Fig 1. Patient flow chart.

Fig 2. Success rates (intent-to-treat population, last observation carried forward) at each timepoint throughout the study. **P = 0.03.

![Graphs showing overall examination](image5.png)

![Graphs showing direct microscopy](image6.png)

![Graphs showing mycological culture](image7.png)

Fig 4. Incidence of negative mycological examination. (a) †P < 0.05, (b) ‡P < 0.01, (c) ⋆P < 0.001 and ‡P < 0.01.
with negative mycological cultures were observed as early as month 3 (94.2% in the AT group vs. 59.7% in the T group; \( P < 0.001 \)), and at months 6, 9, 12 and 15 (Fig. 4c). Figure 5 illustrates the effect of the amorolfine-terbinafine combination on dermatophytic toenail onychomycosis affecting the matrix region during the course of the study.

Two exploratory variables, the presence of streaks and/or of onycholysis at baseline, were analysed for a possible predictive relationship with the overall response rate of the combination therapy at month 18 (Table 3). Patients in the AT group with the presence of streaks at baseline achieved higher success rates (63.6%) than patients in the AT group without streaks (58.2%), while success rates in the AT group were the same with (59.0%) or without (59.3%) the presence of onycholysis. In the T group, success rates were slightly lower in the presence of streaks (44.4% with streaks vs. 45.1% without streaks) and of onycholysis (42.9% with onycholysis vs. 46.0% without onycholysis). However, the study was insufficiently powered for a proper statistical evaluation of these subgroup analyses.

| Table 3 Results of exploratory analyses (presence of streaks and/or onycholysis at baseline and success rate) at month 18 (intent-to-treat population, last observation carried forward) |
|-----------------------------------|------------------|------------------|------------------|
|                                   | Success rate, n (%) | AT group         | T group          | P-value |
| Presence of streaks at baseline   |                  |                  |                  |        |
| No                                |                  | 57 (58.2%)       | 46 (45.1%)       | 0.79   |
| Yes                               |                  | 14 (63.6%)       | 12 (44.4%)       |        |
| Presence of onycholysis at baseline|                  |                  |                  |        |
| No                                |                  | 48 (59.3%)       | 40 (46.0%)       | 0.79   |
| Yes                               |                  | 23 (59.0%)       | 18 (42.9%)       |        |

The AT group received amorolfine + terbinafine, while the T group received terbinafine only.

The quality-of-life assessment was conducted in 39 patients (15.7%) in Italy, Germany and France. Scores decreased similarly in both groups from baseline to endpoint. There was no
difference in quality of life appreciation between the combination and the monotherapy.

Safety evaluation

Both amorolfine and terbinafine were well tolerated during this study. Most adverse events were mild or moderate in severity. Treatment-related adverse events occurred in 15 (11.6%) patients in the T group and 19 (15.9%) patients in the AT group. Only two (1.7%) adverse events were deemed to be related to amorolfine (in-grown toenail and constipation). In total, 40 adverse events related to terbinafine were experienced by 32 (12.9%) patients; the most frequently reported terbinafine-related adverse events were gastrointestinal disorders.

Seven (2.8%) patients discontinued due to adverse events [four (3.3%) in the AT group and three (2.3%) in the T group], all of them deemed to be possibly related to terbinafine. Nine patients (3.6%) experienced 11 serious adverse events during the study, all of which were deemed to be unrelated to study treatments. Laboratory monitoring showed no abnormalities in kidney or liver function.

Cost-effectiveness analysis

In this study, a mean of 3–20 nails per patient were infected. One 5-mL bottle (or two 2.5-mL bottles) allowed for 251 applications,18 deemed sufficient for a 12-month treatment period.

Total costs in all countries involved were shown to be higher for a treatment with the amorolfine-terbinafine combination than with terbinafine alone. However, and because of the significantly higher efficacy of the combination therapy over the same time, costs per cured patient can be considered lower with the amorolfine-terbinafine combination therapy than with terbinafine alone in all studied countries (Fig. 6).

Discussion

Despite the availability of safe and efficacious therapies for onychomycosis, treatment failures with monotherapy are routinely reported and relapses are common, particularly in more extensive, severe cases. Recent in vitro and clinical studies showed that combination therapies with oral and topical antifungal agents can be an attractive option to improve therapeutic efficacy in appropriate patients.15–17 The aim of this study was to assess the efficacy, safety and cost-effectiveness of a combination of amorolfine nail lacquer with oral terbinafine vs. terbinafine monotherapy in a large cohort of patients with dermatophytic toenail onychomycosis and matrix involvement.

Efficacy results confirmed those previously published,19,20 a combination of amorolfine nail lacquer with oral terbinafine enhances treatment efficacy compared with terbinafine alone. The primary efficacy criterion, the success rate (clinical cure and negative direct microscopic examination and negative culture) after 18 months was shown to be significantly higher in the combination group (59.2%) compared with the terbinafine group (45.0%; \( P = 0.03 \)). Secondary efficacy assessments showed similar improvements in favour of the combination group. The study further demonstrated that the impact of the combination in the cure process was visible from month 3 onwards with significantly \( (P < 0.001) \) more patients in the AT group presenting with negative mycological cultures compared with patients in the T group, except for month 18.

Three patients (2.4%) in the terbinafine group were included with onychochrome moulds at study entry. In order to assess the robustness of the ITT analysis, an additional analysis was run on all ITT population except the three patients with onychochrome moulds. It showed that the success rate was still higher with the combination treatment than with the monotherapy (59.2% vs. 46.0%) and this difference was still statistically significant \( (P = 0.04) \).

It was hypothesized that the addition of a topical antifungal treatment directly to the nail plate would improve the response rate over oral therapy alone in patients with important nail invasion by fungi or in those with nail plates separated from the nail bed. Therefore, two exploratory variables, the presence of streaks and/or onycholyis on the target toenail at baseline, were analysed with a view to a possible predictive relationship with the overall response rate obtained with the combination therapy. No statistically significant improvements in overall response rate were observed for combination therapy patients with streaks and/or onycholyis, although the study was not sufficiently powered for a proper statistical evaluation of this subgroup analysis due to the relatively small sample size of the patients with streaks and onycholyis at baseline. However, the numerical increase in success rate for AT patients with streaks (AT group: 63.6% with streaks vs. 58.2% without streaks) warrants further study of this hypothesis in a larger cohort of patients.

The quality-of-life questionnaire was completed in only a limited number of countries, limiting meaningfulness of the
and might have undergone a series of new mycological tests.

Both treatment regimens were safe and well tolerated, with a similar incidence of treatment-related adverse events occurring in both groups (15.9% of patients in the AT group and 11.6% in the T group). All of the adverse events deemed related to the study treatments were secondary to terbinafine, with the exception of two adverse events. Patient tolerance may be a concern with combination therapy; however, the addition of amorolfine nail lacquer to terbinafine therapy did not present an increase in safety risk relative to terbinafine alone in this study, consistent with safety findings in previous studies.16,17

Given the increasing prevalence of fungal nail infections and the associated costs and burden to the healthcare systems, it is important to select the most cost-effective treatments.13 Bearing in mind that a successful long-term strategy should be sought in the treatment of onychomycosis. Indeed, a combination of treatments that are effective in the long term is more cost-effective than a treatment used for a shorter period but with lower long-term efficacy with possible complications related to the relapse or chronicity of the disease, adding to the patient’s overall healthcare costs. The pharmacoeconomic investigation carried out in the present study, accounting for the cure rate as effectiveness measure and based on the public prices, showed that in all participating countries, combination therapy with amorolfine nail lacquer is more cost-effective than oral terbinafine monotherapy. The cost per cured patient with the combination therapy was lower, depending on the country, by up to 15.47% compared with oral terbinafine monotherapy. Only the direct costs of the drugs were considered. Adverse event-related costs were not included as treatments were relatively safe without severe side-effects. Furthermore, we did not consider the cost related to treatment failure. This is a conservative approach as an additional 15% of patients (22 patients) in the terbinafine group compared with the combination group were not cured and thus might have received a new treatment and might have undergone a series of new mycological tests.

In a previous study,16 the cost-effectiveness analysis, comparing the amorolfine-terbinafine combination with terbinafine alone, was conducted only in France. Current study results confirm the findings and extend the analysis to eight other European countries. These results are also in line with recent publications showing that amorolfine in association with terbinafine or itraconazole is more cost-effective than each of these treatments alone.13 The synergy between the two drugs increases the success rate and might improve patient compliance. This study adds to the body of knowledge supporting the finding that combination therapy is the most cost-effective treatment.

The present study results support the existing published data showing the efficacy of combination therapy for the treatment of onychomycosis and confirm the results observed in an earlier pilot study of amorolfine and terbinafine.5,16 There are three noteworthy differences between this study and the previous pilot study: firstly, treatment duration with amorolfine was longer (15 months) in the pilot study than in the presently reported study (12 months); secondly, the primary endpoint of the current study was chosen to set a high threshold for achieving success by combining the measures of cured nail morphology (clinical success) with mycological examination into an 18-month overall response assessment, while the previous study evaluated mycological examination at 3 months as the primary efficacy variable; finally, the duration of the current study was 18 months, 3 months longer than that of the pilot study, reflecting the currently preferred study length to allow sufficient time for toenail regeneration.5

The enhanced overall response with the amorolfine-terbinafine combination results partly from the complementary nature of topical and systemic treatments.3,12 Amorolfine and terbinafine both inhibit the production of ergosterol, but they target different enzymes along the ergosterol biosynthesis pathway. The combination of an oral and a topical agent also provides the benefit of two different routes of administration, targeting the infection at the nail bed via the bloodstream as well as through the nail plate.

In summary, amorolfine nail lacquer, when used in combination with terbinafine in the treatment of dermatophytic toenail onychomycosis with matrix involvement, provides enhanced efficacy relative to terbinafine alone, hence confirming results of a previous pilot study. The addition of amorolfine nail lacquer to terbinafine therapy did not present an increased safety risk relative to terbinafine alone and is more cost-effective than a treatment with terbinafine alone.

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Dedication

This publication is dedicated to the memory of our friend and colleague, Professor Glyn Evans.
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