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Patient-reported outcomes from two randomised studies comparing once-weekly application of amorolfine 5% nail lacquer to other methods of topical treatment in distal and lateral subungual onychomycosis

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Summary

Patient adherence is a key consideration in the choice of a topical regimen for the treatment of onychomycosis. The objective of this study was to investigate patient-reported outcomes (treatment utilisation, adherence and satisfaction) in onychomycosis treated with once-weekly amorolfine 5% nail lacquer versus once-daily ciclopirox 8% nail lacquer (Study A) or once-daily urea 40% ointment/bifonazole 1% cream combination regimen (Study B). Study A: Subjects received amorolfine and ciclopirox on opposite feet for 12 weeks. Study B: Subjects received amorolfine and urea/bifonazole on opposite feet for 6-7 weeks. Assessments included subject adherence as per label, treatment preference and questionnaire. Study A: More subjects adhered to amorolfine (85%) than to ciclopirox (60%) (P = .025). Overall, subjects were satisfied (95% vs 100%, respectively) and the treatments were balanced in terms of preference (50% vs 45%) at week 12. Study B: More subjects adhered to amorolfine dosage (81.8%) than to the dosage of the urea/bifonazole combination regimen (59.1%) (P = .096). At the end of study, 85.7% of subjects preferred amorolfine versus 14.3% for urea/bifonazole. Fewer subjects experienced local side effects with amorolfine (4.5%) compared to urea (27.3%) and bifonazole (15%). Amorolfine 5% nail lacquer offers a simple and convenient treatment option, which may result in improved patient adherence and consequently lead to improved efficacy and patient satisfaction.

KEYWORDS

amorolfine 5% nail lacquer, ciclopirox 8% nail lacquer, onychomycosis, patient adherence, patient-reported outcomes, urea 40% ointment/bifonazole 1% cream

1 | INTRODUCTION

Onychomycosis is a fungal infection of fingernails and toenails which may have a marked effect on patient quality of life.[1,2] It is the most prevalent nail disease accounting for up to 50% of all onychopathies.[3] According to population-based studies, the mean prevalence of onychomycosis in the general population in Europe and North America is 4.3% (95% confidence interval [CI]: 1.9-6.8).[4] Toenails are involved in the majority of cases due to the slow growth and increased exposure to injury, facilitating the establishment of fungal infection.[5] Dermatophytes are responsible for most cases (65%) of onychomycoses.[4] There are several variants of onychomycosis described in the

literature, with distal and lateral subungual onychomycosis (DLSO) being the most frequent variation.[6,7] Onychomycosis is characterised by evident changes to the nail such as dyspigmentation, onycholysis and nail plate thickening. These changes result in substantial embarrassment for the patient, which deters many from consulting a physician until the disease progresses to more severe states or impairs daily life.[8-10]

The availability of non-prescription topical antifungal agents facilitates the use of effective and well-tolerated treatments in the early stages of fungal nail infection. Amorolfine 5% nail lacquer, ciclopirox 8% nail lacquer, urea 40% ointment and bifonazole 1% cream are available over the counter (OTC) worldwide. Adherence to treatment is the process by which patients take their medications as prescribed (or recommended in the label).[11] Adherence to topical antifungal therapy for the treatment of onychomycosis has a major influence on outcome.[12] A Chinese study showed that the cure rate of onychomycosis in patients with good adherence was 63% (58/92), whereas in non-adherent patients this rate was merely 2% (6/293).[12] Several adherence studies in chronic dermatoses such as psoriasis, atopic dermatitis or rosacea have shown that ensuring a good adherence to topical therapy is as important as reaching the correct diagnosis and selecting the appropriate treatment.[13-17] Treatment of toenail onychomycosis may require a lengthy course of therapy and thus, patient adherence is a key consideration in the choice of a topical regimen. Patient adherence to long-term topical treatment may depend not only on the efficacy of the treatment but also on the ease of use, application procedure and tolerance. Such factors include inconvenient or time-consuming application of medication, ambiguous/complicated usage instructions or side effects such as irritation, burning and dryness.[18,19] These subjective factors are infrequently assessed in prospective randomised studies.

Mild-to-moderate onychomycosis can be effectively and safely treated with topical antifungals, a number of which can be purchased OTC with the advice of pharmacists.[20] Hence, with self-treatment, convenience of use is essential to avoid discouragement or inappropriate treatment application.

Amorolfine 5% nail lacquer (Loceryl® 5% Nail Lacquer; Galderma, Lausanne, Switzerland) is a broad-spectrum topical antimycotic, indicated for the treatment of onychomycosis without matrix involvement. The advantage of this agent is the persistent antifungal effect on the nail bed, allowing a once-weekly application as recommended in the product label. Filing of the nail plate is performed, prior to application, to increase the penetration of amorolfine to the nail bed, where most fungi reside.[21-25]

Ciclopirox 8% (Ciclopoli® Nail Lacquer; Taurus Pharma, Bad Homburg, Germany) is another broad-spectrum topical antimycotic which, according to the label recommendation, must be applied daily. No filing is recommended for this treatment.

The combination regimen of urea 40% ointment and bifonazole 1% cream (Canesten® Fungal Nail Treatment Set; Bayer, Pymble, Australia) provides chemical nail ablation followed by topical antifungal treatment. Urea 40% ointment under occlusion possesses keratolytic properties and is indicated for the softening and removal of the diseased/dystrophic nails in onychomycosis.[26,27] Bifonazole 1% cream is a broad-spectrum imidazole with antifungal activity, rubbed into the nail bed after nail debridement.[28] According to the label recommendation, the urea/bifonazole regimen must be applied on a daily basis. The duration of treatment is 6-7 weeks and comprises two phases: 2-3 weeks for debridement of the affected nail with the urea 40% ointment followed by 4 weeks of antifungal treatment with bifonazole 1%.[29]

These currently available OTC topical antifungals offer different treatment modalities including daily or weekly application, or removal of the diseased nail.

The objective of the two randomised comparative clinical studies presented in this article was to investigate the influence of these different treatment modalities on patient-reported outcomes (treatment utilisation, adherence and satisfaction) in DLSO treated with once-weekly amorolfine versus once-daily ciclopirox (Study A) or once-daily urea/bifonazole (Study B).

2 | SUBJECTS AND METHODS

2.1 | Study design

The studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. They were approved by institutional review boards, and all subjects provided written informed consent prior to study procedures.

2.1.1 | Study A (amorolfine 5% vs ciclopirox 8%)

This was a single-centre, randomised, investigator blinded, active controlled, intra-individual, Phase IV study. The study involved subjects aged 18 years or older with a mycologically confirmed DLSO, and less than 80% of the nail surface area involved on at least one toenail of each foot, without matrix involvement.

Subjects were randomised on a 1:1 ratio to receive once-weekly amorolfine nail lacquer (after nail filing) for 12 weeks on the affected toenails of one foot and ciclopirox nail lacquer once daily for the same duration on the opposite foot after nail preparation. Prior to each application of amorolfine nail lacquer on the nail plate, subjects were required to remove any former varnish layers with a nail varnish remover and subsequently file the surface of the nail (particularly the affected area) as thoroughly as possible. Ciclopirox nail lacquer was applied to the entire nail plate and surrounding skin of affected toenails, after removing the free toenail edge and diseased toenail with a nail clipper, if necessary. This study comprised visits at screening, baseline and weeks 4, 8 and 12.

2.1.2 | Study B (amorolfine 5% vs urea 40%/bifonazole 1%)

This was a single-centre, randomised, open-label, active controlled, intra-individual, Phase IV study. The study involved subjects aged 18 years or older with mycologically confirmed DLSO affecting no

more than 50% of the surface (from the nail edge) of at least one great toenail of each foot, without matrix involvement.

Subjects were randomised on a 1:1 ratio to receive amorolfine nail lacquer once weekly for a maximum of 7 weeks on the affected toenails of one foot and urea/bifonazole combination regimen, for the same duration on the opposite foot. Subjects in the latter group received urea 40% ointment under occlusion, daily for the first 2-3 weeks (phase I: removal of diseased nail). The procedure consisted of soaking the foot for 10 minutes in warm water, and subsequently removing the softened infected nail using a plastic nail scraper and applying the ointment on the nail prior to occlusion under a plaster. Following the removal of the diseased nail plate, the treatment consisted of daily bifonazole 1% cream application for the remaining 4 weeks (phase II: treatment of infection).

This study included visits at screening, baseline and weeks 2, 3 and 6 or 7, depending on the duration of phase I.

2.2 | Assessments

2.2.1 | Study A

- Subject adherence to study treatments as per label (Summary of Product Characteristics [SmPC]) via completed subject diary:
  - Adherence rate as per label: Percentage of subjects "in and off label".
  - Non-adherence count as per label: number of "off label" episodes.
- Subject preference for study treatment at each postbaseline visit.
- Subject questionnaire at last visit.
- Incidence of adverse events (AEs) throughout the study.

2.2.2 | Study B

- Subject adherence with study treatments as per label (SmPC) via completed subject diary:
  - Adherence rate as per label: Percentage of subjects "in and off label".
  - Non-adherence count as per label: number of "off label" episodes.
- Subject preference at the end of phase I (week 2 or 3) and phase II (week 7 or early termination).
- Subject questionnaire at the end of each phase:
  - Phase I: At week 2 if complete removal of diseased nail plate was achieved, or at week 3 if continued application of urea was required for one additional week.
  - Phase II: At week 7/early termination.
- Urea/bifonazole procedure performance:
  - Assessment of diseased toenail plate removal success rate by subjects and the investigator.
- Incidence of AEs throughout the study.

2.3 | Randomisation and sample size

For both studies, randomisation lists were generated by a statistician and transmitted to the assigned clinical packaging organisation for labelling. The RANUNI routine of the Statistical Analysis System (SAS Institute Inc., Cary, NC, USA) was used for the randomisation lists.

The randomisation lists and electronic files were secured in a locked cabinet with restricted access to only the designated personnel directly responsible for labelling and handling the study treatments.

No statistical rationale of sample size was necessary for these studies, as no inferential statistics were performed.

2.4 | Statistical analysis

Categorical variables, quantitative variables and subject's preference for treatment were analyzed using the McNemar test, paired Wilcoxon signed-rank test and sign test, respectively. The .05 probability level was chosen to declare significance. Demographic data, baseline characteristics and safety data were descriptively summarised. No missing values were replaced (observed data only).

3 | RESULTS

3.1 | Subject disposition

Subject disposition of both studies is presented in Figure 1.

3.1.1 | Study A

The study was conducted at one centre in Tübingen, Germany from September 2015 to June 2016. A total of 20 subjects with a mean age of 54.5 years were enrolled and all of them completed the study. Subjects had a mean of 1.9 affected toenails per foot (Table 1).

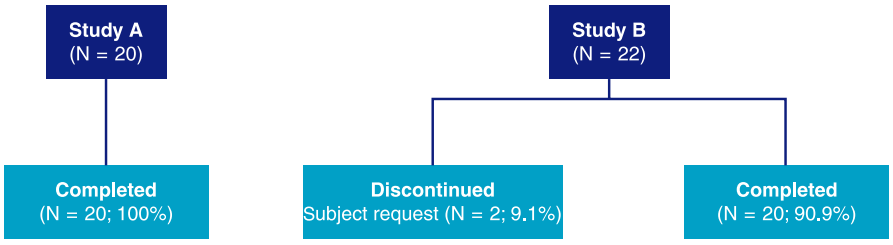

FIGURE 1 Subject disposition

TABLE 1 Demographics and baseline disease characteristics (intent-to-treat population)

		Study A Total (N = 20)	Study B Total (N = 22)
Age (years)	N	20	22
	Mean±SD	54.5 ± 8.7	55.3 ± 12.6
	Min~Max	30~72	31~79
Gender	N	20	22
	Female	10 (50%)	5 (22.7%)
	Male	10 (50%)	17 (77.3%)
Race	N	20	22
	Caucasian	20 (100%)	22 (100%)
Skin phototype	N	20	22
	I	-	1 (4.5%)
	II	20 (100%)	4 (18.2%)
	III	-	14 (63.6%)
	IV	-	3 (13.6%)
Number of affected nails	Mean±SD	1.9 ± 1.4	3.2 ± 1.7
Direct microscopic examination	Positive	20 (100%)	22 (100.0%)
Culture	Positive	20 (100%)	22 (100.0%)

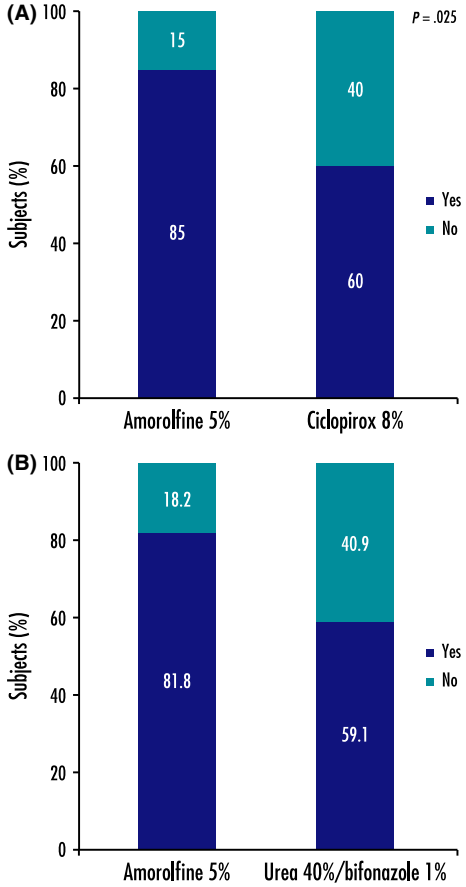

FIGURE 2 Subject adherence as per label for (A) Study A and (B) Study B (intent-to-treat population)

3.1.2 | Study B

The study was conducted at one centre in Reykjavik, Iceland, from January 2016 to September 2016. A total of 22 subjects with a mean age of 55.3 years were enrolled. Of those, 20 subjects (90.9%) completed the study. Two subjects discontinued the study by request. Overall, subjects had a mean of 3.2 affected toenails per foot (Table 1).

3.2 | Patient-reported outcomes

3.2.1 | Study A

Subject adherence as per label: In the intent-to-treat (ITT) population, significantly more subjects adhered to the respective label with amorolfine (85%) than with ciclopirox (60%) (P = .025) (Figure 2A). One subject in the amorolfine group missed 2 applications versus 8 subjects in the ciclopirox group with a mean of 3 missed applications (P = .008).

The reason for missing the application of amorolfine, as reported by the subject, was "forgot to use the treatment". Subjects who missed applications of ciclopirox reported they "forgot to use the treatment" (5 subjects, 62.5%), "were away from home" (5 subjects, 62.5%) and "did not have time to apply the treatment" (1 subject, 12.5%).

In terms of overall preference, at week 12 the two treatments were balanced (50% vs 45%, respectively) without statistically significant difference at weeks 4, 8 or 12 (Figure 3A).

Based on the satisfaction questionnaire at the end of the study, subjects reported that for the treatment of an average of two nails per foot, amorolfine took longer to apply compared to ciclopirox (5.1 vs 2.6 minutes per application, respectively; P < .001). However, the total application time per week was approximately 3.5-fold longer for ciclopirox than for amorolfine (18.2 vs 5.1 minutes). There was no statistically significant difference between treatments with respect to satisfaction with the frequency of application (55% vs 40% very satisfied with amorolfine and ciclopirox respectively) (Figure 4A) and ease of use (45% per group found the treatment very easy to use) (Figure 4B). Subjects were overall satisfied with both amorolfine and ciclopirox (95% vs 100%, respectively) (Figure 4C). Ninety per cent of subjects considered continuing the use of amorolfine compared to 75% of subjects for ciclopirox. Approximately 80% of subjects stated they would recommend both products to family or friends.

3.2.2 | Study B

Subject adherence as per label: More subjects were adherent as per label with amorolfine than with the urea/bifonazole regimen (81.8% vs 59.1%, respectively, P = .096) (Figure 2B). One subject in the amorolfine group missed a single application, whereas 3 subjects overused

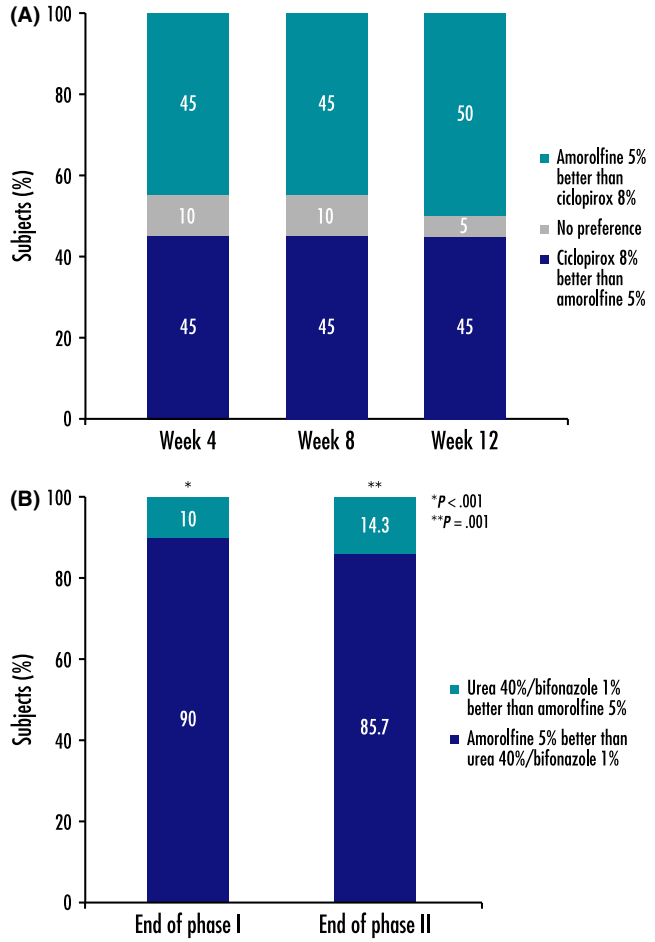

FIGURE 3 Subject overall preference for (A) Study A and (B) Study B (intent-to-treat population)

the product. In the urea/bifonazole group, 9 subjects missed a mean of 2 applications (between 1 and 4). In non-adherent subjects, the mean number of missed applications was significantly higher for urea/bifonazole than for amorolfine ($P = .008$).

The reason for missing the application of amorolfine was a non-related AE (accident). Most common reasons for missing the application of urea included "being away from home" (44.4%), "did not have time to apply" (33.3%), "forgot to use" (22.2%), "tired of applying" (22.2%), "procedure too difficult to follow" (22.2%), and "local tolerance" (11.1%). For bifonazole, the most common reasons for missing applications included "forgot to use" (33.3%), "being away from home" (33.3%), "did not have time to apply" (11.1%) and "tired of applying" (11.1%).

Subject adherence in terms of nail preparation procedure: More subjects adhered to the nail preparation procedure for amorolfine (nail filing) than for urea/bifonazole (nail debridement) (86.4% vs 22.7%, respectively, $P < .001$). Significantly more "off label" episodes, in terms of nail preparation, were reported for urea/bifonazole (17 subjects with a mean of 3 episodes) than for amorolfine (3 subjects with a mean of 1 episode) ($P < .001$).

Urea/bifonazole procedure performance: At the end of the urea treatment (week 3), of 65 treated nails, 25 (38.5%) had been incompletely removed and the residual diseased toenails needed to be removed by the investigator.

In terms of subject overall preference, at the end of phase I, 90% preferred amorolfine and 10% preferred urea. At the end of phase II, the vast majority of subjects (85.7%) preferred amorolfine and 14.3% preferred bifonazole (Figure 3B).

The subject questionnaire at the end of the study phases showed that, over the course of a week, the application of amorolfine took significantly less time compared to nail debridement with urea during phase I (12.4 min/week vs 156.1 min/week, respectively, $P < .001$), and daily applications of bifonazole during phase II (10.3 min/day and week vs 7.6 min/day and 53.2 min/week, respectively). Nearly all subjects were satisfied/very satisfied with the frequency of amorolfine applications compared to those of urea during phase I and bifonazole during phase II of the treatment (95.4% vs 54.6% and 95% vs 70%, respectively) (Figure 4D). Overall, more subjects found the application of amorolfine easy/very easy compared to that of urea and bifonazole (95.5% vs 45.5% during phase I and 95% vs 75% during phase II) (Figure 4E). Subjects were overall satisfied/very satisfied with the use of amorolfine vs urea, and vs bifonazole (90.9% vs 81.8% during phase I, 100% vs 90% during phase II, respectively) (Figure 4F). Fewer subjects experienced local side effects with amorolfine (1 subject, 4.5% during phase I; 1 subject, 5% during phase II) compared to urea (6 subjects, 27.3% during phase I) and bifonazole (3 subjects, 15% during phase II) (Figure 4G).

At the end of the study, nearly all subjects would recommend the use of both amorolfine and urea/bifonazole (100% vs 89.5%, respectively). At end of study, all subjects (100%) considered to use amorolfine for 7-10 additional months compared to 85% for urea/bifonazole.

3.3 | Safety

None of the AEs reported in these studies, other than expected local reactions, were considered to be treatment related and none led to treatment discontinuation. All AEs were mild to moderate in severity.

4 | DISCUSSION

Good adherence to appropriate therapy remains critically important for the prevention of treatment failure, disease progression and treatment escalation in dermatology.[30] The two Phase IV studies discussed in this article investigated patient-reported outcomes (utilisation, adherence and satisfaction) following treatment with OTC topical antifungal agents: once-weekly amorolfine versus once-daily ciclopirox (Study A) or once-daily urea/bifonazole (Study B) in patients treated for DLSO. The three treatments compared in this study can be purchased OTC and need to be patient friendly to ensure good adherence.

In Study A (amorolfine vs ciclopirox), more subjects adhered to the instructions for use as per label for amorolfine than for ciclopirox. The main reasons for non-application of study treatments were that the

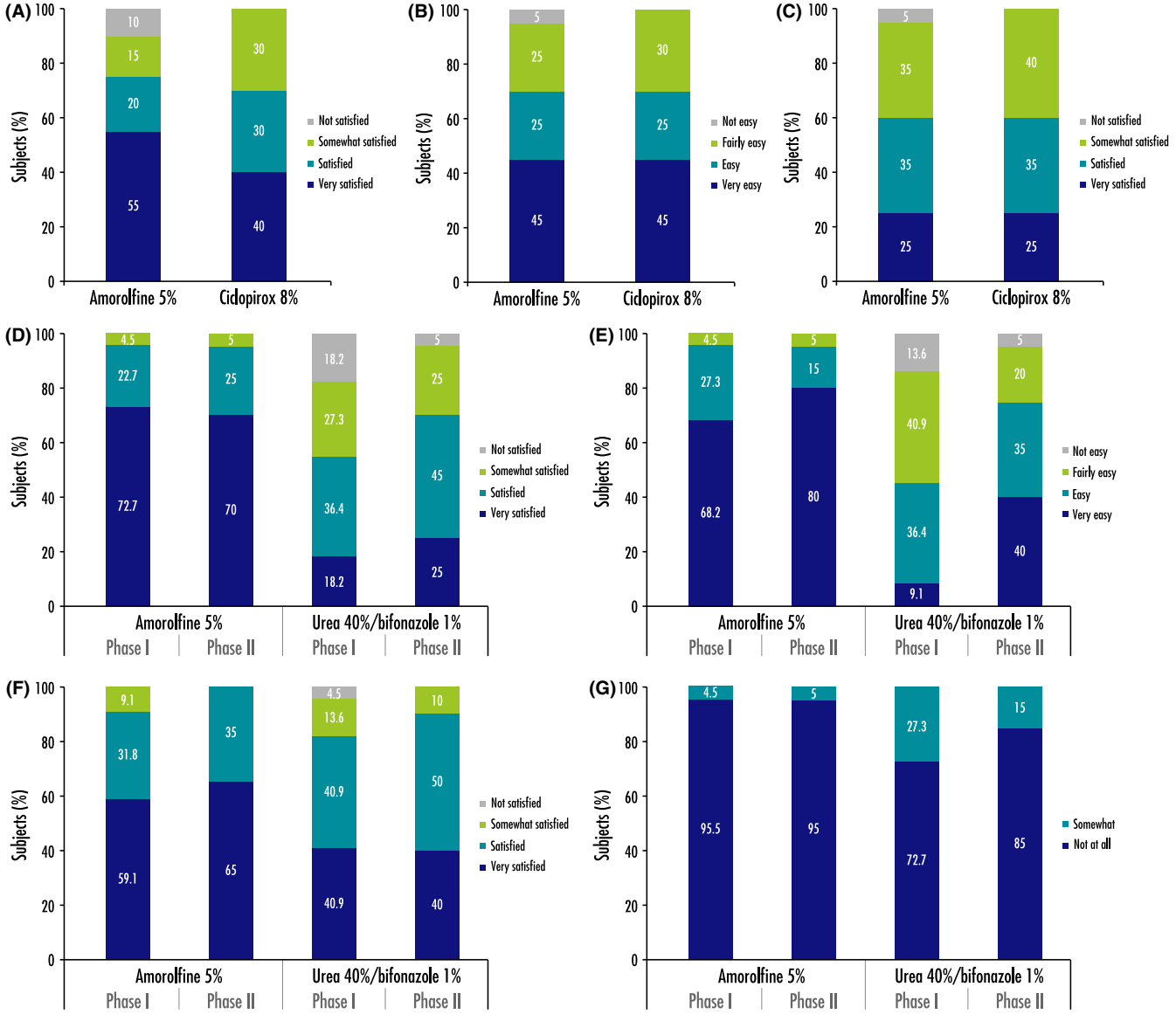

FIGURE 4 Subject questionnaire for Study A: (A) frequency of application, (B) ease of use and (C) overall satisfaction; and Study B: (D) frequency of application, (E) ease of use, (F) overall satisfaction and (G) local side effects

subjects forgot to use the treatments or that they were away from home. Subjects had no preference for either of the study treatments, although more subjects considered continuing to use amorolfine rather than ciclopirox after 12 weeks of use.

According to the questionnaire at last visit, subjects reported that amorolfine nail lacquer after filing took longer to apply than ciclopirox nail lacquer (without filing) ($P < .001$) and was less easy to spread ($P = .008$). Although the application procedure for amorolfine is slightly longer than for ciclopirox, it is carried out once weekly, whereas the procedure for ciclopirox must be carried out once daily. There was no statistically significant difference, over this 12-week study period, between treatments regarding satisfaction with the frequency of application and ease of use.

The results of Study B (amorolfine vs urea vs bifonazole) indicated that subject adherence was better for amorolfine compared to urea/bifonazole. More subjects preferred amorolfine compared to urea/bifonazole. In addition, more subjects were satisfied with the frequency of applications, ease of use and treatment application time for amorolfine than for urea/bifonazole.

Difficulty to follow the procedure and concerns for tolerance were among the primary reasons for not following the urea/bifonazole treatment procedure as per label. The complete ablation of softened diseased nail by the urea ointment was not effective for nearly half of treated nails after 2 weeks and required intervention by the investigator after the third week for the removal of the residual nail plate in nearly 40% of treated nails.

Incomplete nail debridement following daily application of urea ointment for 2-4 weeks is a determinant factor for efficacy and is therefore considered an exclusion criterion when studying the efficacy of bifonazole cream in onychomycosis.[31] Although urea ointments are

available OTC, the success rate of home debridement, without the support of a health professional, remains largely unexplored. Based on the available evidence, home debridement with urea ointment may be challenging, with reported failure to completely debride the affected nail area after 3 weeks ranging between 40%-60%.[26] A previous study on onychomycosis, comparing the efficacy of urea and bifonazole alone to that of the same local therapy combined with short-term oral griseofulvin, showed that the mean time to detachment of the diseased nail was longer than the recommended 2-3 weeks of treatment (24.9 days).[32] The findings of Study B discussed in this article confirm the limitations of home treatment for complete nail debridement with urea ointment.

All three treatment regimens showed a favourable safety profile with no treatment-related AEs or AEs leading to discontinuation.

A shortcoming of these studies is the limited duration of treatment for amorolfine and ciclopirox compared to their usual course of therapy (9-12 months). Therefore, on this occasion, it was not possible to assess the impact of treatment efficacy and duration on subject adherence.

Collectively, the results of these two studies demonstrated that subjects found the once-weekly application of an antifungal nail lacquer with prior nail filing significantly easier to follow than chemical nail debridement. Fewer applications were missed with weekly applications of amorolfine nail lacquer than with daily applications of ciclopirox nail lacquer or bifonazole cream. Thus, the once-weekly administration of amorolfine nail lacquer may facilitate patient adherence to treatment and improve patient satisfaction, which are important factors for efficacy with an OTC treatment.

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CONFLICT OF INTEREST

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